Prescribing In Elderly People 2

The challenge of managing drug interactions in elderly people

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Drug therapy is essential when caring for elderly patients, but clearly it is a double-edged sword. Elderly patients are at high risk of having drug interactions, but the prevalence of these interactions is not well documented. Several types of interactions exist: drug–drug, drug–disease, drug–food, drug–alcohol, drug–herbal products, and drug–nutritional status. Factors such as age-related changes in pharmacokinetics and pharmacodynamics, frailty, interindividual variability, reduced homoeostatic mechanisms, and psychosocial issues need to be considered when drug interactions are assessed. Software can help clinicians to detect drug interactions, but many programmes have not been updated with the evolving knowledge of these interactions, and do not take into consideration important factors needed to optimise drug treatment in elderly patients. Any generated recommendations have to be tempered by a holistic, geriatric, multiprofessional approach that is team-based. This second paper in a series of two on prescribing in elderly people proposes an approach to categorise drug interactions, along with strategies to assist in their detection, management, and prevention.

Introduction

The increasing number of elderly patients traversing the health-care system creates new challenges since they have special needs. Appropriate prescribing is one of these challenges, and was discussed in the first paper in the series. In this paper, the challenge of managing drug interactions will be addressed.

Elderly patients are at high risk of drug interactions. They frequently take many drugs, have several comorbidities, and might not maintain adequate nutritional status. The application of evidence-based medicine tends to increase the number of drugs prescribed to treat one disorder. Furthermore, the product of successful health care has created a new group of patients with organ transplantation, mental-health problems, and HIV who have survived to late life. Patients with these disorders are taking new classes of medications that are commonly associated with drug interactions. Additionally, several factors, such as interindividual variability, frailty, and reduced homoeostasis, increase the complexity of management of drug interactions in elderly people.

Although the actual incidence and prevalence of adverse drug events caused by drug interactions in elderly people is uncertain, they represent an important health problem and are generally preventable. For example, Gurwitz and colleagues reported that 13% of preventable prescribing errors detected in ambulatory patients involved drug interactions. A study showed an increase in morbidity and mortality associated with hyperkalaemia in elderly patients with heart failure. The interaction between spironolactone and angiotensin-converting-enzyme (ACE) inhibitors or other medical disorders that increase the risk of hyperkalaemia certainly contributed to the results, and most events could probably have been prevented. The objectives of this paper are to inform clinicians of the various drug interactions potentially occurring in elderly patients, to review how they could lead to adverse drug events, and to propose strategies for their detection, management, and prevention.

Classification and lists of drug interactions

A drug–drug interaction can be defined as the effect that one drug has on another. Drug–drug interactions can be pharmacokinetic or pharmacodynamic in nature, and are not exclusive to the elderly population. Pharmacokinetics (what the body does to the drug) involve the effects of one drug on the absorption, distribution, metabolism, or excretion of another drug. These interactions can result in changes in serum drug concentrations and might change clinical response. The most frequent pharmacokinetic drug–drug interactions involve several isoenzymes of the hepatic cytochrome P450 (CYP) and drug transporters such as the P-glycoprotein and organic anion transporters. Pharmacodynamics (what the drug does to the body) is related to the pharmacological activity of interacting drugs. The outcome is an amplification or decrease in

Search strategy and selection criteria

Examples of different types of drug interactions in elderly patients

<table>
<thead>
<tr>
<th>Example</th>
<th>Mechanism of action</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-drug, PK</td>
<td>Gatifloxacin + calcium and antacid</td>
<td>Decrease in absorption of gatifloxacin</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin + olanzapine</td>
<td>Ciprofloxacin inhibits CYP1A2 leading to an increase in Cp of olanzapine</td>
</tr>
<tr>
<td>Drug-drug, PD</td>
<td>Ciprofloxacin + glibenclamide</td>
<td>Synergy (hypoglycaemic effect)</td>
</tr>
<tr>
<td></td>
<td>Anticholinergic drug + donepezil</td>
<td>Antagonism</td>
</tr>
<tr>
<td>Drug-nutritional status</td>
<td>Low albumin + phenytoin</td>
<td>Increase in free phenytoin concentration</td>
</tr>
<tr>
<td>Drug-herbal product</td>
<td>Gingko + aspirin</td>
<td>Decrease in platelet function and adhesion</td>
</tr>
<tr>
<td>Drug-alcohol</td>
<td>Alcohol + chronic use of bromazepam</td>
<td>Synergy</td>
</tr>
<tr>
<td>Drug-disease or drug-patient</td>
<td>Metoclopramide for gastric dysmotility in a patient with Parkinson’s disease</td>
<td>Increase in dopamine receptor blockade</td>
</tr>
</tbody>
</table>

Cp = plasma concentration. CYP = cytochrome P450. PD = pharmacodynamic. PK = pharmacokinetic.

Table: Examples of different types of drug interactions in elderly patients

The therapeutic effects or side-effects of a specific drug. Other types of drug interactions are drug-food, drug–alcohol, drug–herbal product, or drug–nutritional status interactions. Finally, drug–disease or drug–patient interactions take place when a drug has the potential to exacerbate an underlying disease or medical disorder. The table provides some examples of different types of drug interactions and adverse outcomes that can be seen in elderly patients. Several groups of clinicians and researchers have attempted to develop lists of drug–drug and drug–disease interactions that should be avoided in elderly people. There is only partial convergence between the lists. Dietary supplements, alcohol, and herbal remedies have generally not been included. Since some drugs have limited availability because of formulary restrictions or are now rarely prescribed for elderly patients, these lists need to be adapted to local practice.

Why are elderly patients at higher risk of drug interactions?

Increased risk of drug interactions might be because of patient factors, prescriber factors, or difficulties within the health-care system such as inefficient communication between health professionals and patients.

Age-related pharmacokinetic and pharmacodynamic changes can potentially increase the risk of adverse events from drug interactions. Cellular, organ, and systems reserves decrease with age. The effects of individual genetics, lifelong living habits, and environment will result in heterogeneity between people as they age. Thus, all 85-year-old women are not going to react to the same specific dose of a drug in the same way. The prototypical man weighing 70 kg used in modelling adult medicine and response to treatment is not applicable to elderly patients. The risk of drug interactions increases with the number of drugs prescribed and elderly people use more drugs than do younger adults. For example, in 2005, CAD$24.8 billion was estimated to be spent in Canada on drugs, of which 44% were prescribed to those aged 65 years and older.

Physicians are often not aware of all the drugs their elderly patients are taking. Frank and colleagues reported that, in 37% of cases, patients were taking drugs without their physicians’ knowledge, and 6% of patients were not taking medications that were on their physicians’ lists. Incomplete documentation of past medical history and active drug profile means that emergency physicians are not considering interactions as a possible cause of the presenting complaints of elderly patients. Furthermore, atypical presentation of disease or vague presenting complaints such as confusion, falls, urinary incontinence, and weakness could mask or confuse the detection of drug interactions.

Elderly patients might receive prescriptions from several physicians and take them to be filled at many pharmacies. Tamblyn and co-workers have shown that the risk of receiving an inappropriate drug combination is directly related to the number of physicians prescribing drugs for that elderly patient.

How common are drug interactions in elderly patients?

Several studies have measured the prevalence of drug interactions in elderly patients. Studies looking at potential interactions should be distinguished from those assessing actual interactions (i.e., with an adverse patient outcome as a result from the drug interaction). Potential drug interactions are usually detected with computerised detection programmes flagging drug interactions. In a European study of 1601 elderly outpatients living in six European countries, 46% of patients had at least one potential clinically significant drug–drug interaction, and 10% of these interactions were regarded as of high severity. Davies and colleagues found that 25% and 11% of patients on elderly psychiatric wards were prescribed a clinically relevant potential drug–drug interaction involving cytochromes 2D6 and 3A4, respectively. High rates of interactions between drugs and herbal remedies or alcohol were also reported. In a small study with elderly patients attending a memory clinic, at least a third were at risk from a potential herb–drug interaction. Pringle and co-workers reported that 19% of patients were using concomitant alcohol and alcohol-interactive prescription drugs. Lindblad and colleagues assessed drug–disease interactions in a group of frail elderly patients in hospital, with two different lists of criteria. They reported that 15–40% of patients had a potential drug–disease interaction, the most common being calcium-channel blockers in patients with heart failure, β blockers in those with diabetes, and aspirin in those with peptic ulcer disease. The use of several
prescription drugs and a higher comorbidity index were significantly associated with having one or more potential drug–disease interactions.45

These results should be interpreted cautiously for several reasons. First, there is a large variability in how drug interactions are defined, their clinical importance, and the sources used to detect them. Depending on the criteria used, prevalence rates can be very different, which can lead to misunderstandings if interactions are not assessed carefully.46 Second, many potential drug interactions never lead to an actual clinical effect. The above prevalence rates might, therefore, overestimate the true clinical significance of the problem. Hohl and colleagues46 assessed the frequency of adverse drug events leading to an emergency room visit. Although 31% of the study population had a potential high-risk drug–drug interaction, not one adverse drug event that was identified was caused by a drug interaction. Third, drug–drug interaction databases are not geriatric-specific. Fourth, the validity of some criteria of drug–disease interactions, such as the use of β blockers in patients with diabetes, is debatable. Finally, studies had enrolled patients with varying comorbidities, which can affect the outcomes. Future studies should aim to focus on drug interaction criteria that have sufficient clinical significance, and link prescribing data with adverse outcomes if feasible; they should be regularly updated; and be relevant to the situations seen in elderly patients—eg, the concomitant use of anticholinergics and acetylcholinesterase inhibitors.46,47

Studies that focus on drug interactions leading to adverse patient outcomes (ie, actual drug interactions) do provide a better idea of the true prevalence of the problem, but again the criteria selected to detect interactions can lead to different results. A study in France49 showed that half of patients admitted to hospital had at least one potential drug–drug interaction, but that this interaction led to an adverse drug event in a quarter of patients. The most frequent adverse drug events were neuropsychological impairment, hypotension, and acute renal failure. As expected, the prevalence is lower for adverse drug interactions than it is for potential drug interactions, but outcome can be severe (eg, hospital admission).49 Juurlink and co-workers51 reported that many admissions of elderly patients for drug toxic effects occur after administration of a drug known to cause drug–drug interactions, and that many of these interactions could be avoided. For example, patients admitted with toxic effects from digoxin were 12 times more likely to have been given clarithromycin in the week before admission, and patients on ACE inhibitors admitted for a diagnosis of hyperkalaemia were 20 times more likely to have been given a potassium-sparing diuretic in the previous week.51 Hanlon and colleagues52 showed that 6% of elderly inpatients had a drug–drug interaction with a detectable adverse outcome, and that 20% of these patients had an actual drug–disease interaction. With the same instrument (medication appropriateness index) to detect drug interactions, a group of Australian researchers also reported that actual drug–disease interactions were two to three times more frequent than actual drug–drug interactions.53 To the best of our knowledge, there are no...
published data for the prevalence of actual drug–food, drug–alcohol, and drug–herbal product interactions. There are several reasons to argue that the prevalence of actual drug interactions could be underestimated. First, the link between adverse drug events and underlying drug interaction is probably under-recognised and frequently attributed to other comorbid disorders. Health-care professionals might not suspect that an elderly patient’s new symptoms are attributable to an underlying drug interaction. Second, some drugs are prescribed as needed and can potentially create transient or sporadic drug–drug interactions. Prescribers might not be aware if or when these drugs are taken, and drug interactions then become more difficult to detect. Third, the coding of clinical data in administrative systems can conceal drug interactions as a causative factor. For example, a patient who develops salt and water retention as a result of taking a non-steroidal anti-inflammatory drug (NSAID) would be admitted with the diagnosis and coding for heart failure rather than adverse drug event or drug interaction.

A simple clinical approach to address drug interactions in elderly people

The understanding and management of drug interactions in elderly people can be challenging. We propose a simple clinical approach to address this confusing area. The first category includes drug interactions that are common. Drug–drug interactions are frequent when drugs with a narrow therapeutic index such as digoxin, phenytoin, or warfarin are used. Drug interactions in this category are generally well known, have a readily available laboratory monitoring test, and are detected by all commercial drug interaction software systems. Furthermore, drugs that are substrates, inhibitors, or inducers of CYP450 isoenzymes (eg, CYP3A4, CYP2D6) are also commonly involved in drug–drug interactions. Pharmacokinetic and drug interaction software, as well as discussion with the pharmacist, can usually alert the prescriber to potential difficulties. Furthermore, diseases or disorders such as constipation, dementia, and postural hypotension are frequently involved in drug–disease interactions.

The second category is complex interactions. Patients with nine or more drugs and five or more comorbidities frequently fall into this category. The choice of drugs used to manage every disorder is usually appropriate when considered individually. However, the total combination could yield unwanted results in terms of drug–drug and drug–disease interactions, as shown in panel 1 and a case report. 6,16

The third category is cascade interactions. The prescribing cascade begins when an adverse drug reaction is misinterpreted as a new medical disorder. Another drug is then prescribed, and the patient is placed at risk of developing additional adverse effects relating to this potentially unnecessary treatment. A prescribing cascade can produce a pharmacokinetic or pharmacodynamic interaction. For example, a study reported that patients with dementia who were dispensed cholinesterase inhibitors had an increased risk of receiving an anticholinergic drug to manage new urinary incontinence. 17 Panel 2 shows another example of the prescribing cascade. A complete and careful history of the onset of a patient’s symptoms and recent treatment changes are usually diagnostic.

Can information technology software help clinicians manage drug interactions?

One of the outcomes of quality improvement in health-care has been the increasing use of information technologies to keep patient injury caused by drug errors and interactions to a minimum. 4,5 Potential drug interactions can be

Panel 3: Questions to help the clinician to detect drug interactions

1 Identification of the nature of the interaction
   • Is there a potential interaction between a drug and another drug, disease, food, nutrition, or a combination of any of these factors?

2 Understanding the mode of action of the interaction
   • Can the pharmacokinetic interaction be explained in terms of absorption, distribution, metabolism, or elimination of the drug?
   • Is the interaction pharmacodynamic?
   • What is the time course of the interaction? Several factors will affect the time course of the interaction, such as the mechanism of the interaction, the pharmacokinetics of the object drug, the nature of interacting drug (inhibitor, inducer, substrate), the sequence of prescription, and the baseline concentration of the target drug.
   • Is this interaction well documented in published work, or are there strong suspicions (theoretical or clinical) to expect that an adverse drug interaction might take place?
   • Would the potential interaction appear when a drug is added or discontinued?

3 Identification of potential or real clinical outcomes for the patient
   • What are the short and long-term clinical outcomes for the patient?
   • Is the patient having new problems (eg, falls and gait difficulties, bleeding, blood pressure changes, confusion) that can be explained by a drug interaction?
   • Does the patient have risk factors that might increase the likelihood of an adverse outcome (eg, with regard to comorbidities, other drugs taken, dose and duration of treatment, pharmacogenetics)?

4 Monitoring and follow-up for potential drug interactions
   • Is an appropriate monitoring plan in place—eg, INR, serum drug concentration, electrolytes, blood pressure, glucose concentration, and who is responsible for follow-up to promote continuity of care? Does this plan account for the estimated time course of the interaction?
   • Are caregivers vigilant to monitor for the appearance of new symptoms after any changes to drug treatment?
   • Has the drug interaction been documented in the patient’s medical record?

*For example, a patient on chronic treatment with a drug that induces CYP3A4 (eg, rifampicin) who is then given a CYP3A4 substrate will experience little or no effect from the CYP3A4 substrate, starting with the very first dose of the substrate. If, however, the same two drugs are given but the inducer is added to the substrate, the interaction will take much longer to develop. Another example would be a patient who is just on the verge of toxic effects from drug A when an inhibitor of drug A’s metabolism is added (drug B). Drug A might normally take days to achieve a new steady-state serum concentration when drug B (an inhibitor of drug A) is added. In most people, the interaction would be delayed. However, if the patient was only a few drug molecules away from toxicity, he may develop toxic effects in less than 24 h. For example, a patient on warfarin who is started on thyroid supplement for hypothyroidism is at greater risk of overanticoagulation and bleeding than a patient on chronic thyroid supplement treatment who is started on warfarin. For example, it can take 7–10 days for the international normalised ratio (INR) to stabilise after a patient on warfarin starts taking a CYP2C9 inhibitor.
Panel 4: Actions for management of drug interactions

1. If possible, discontinue the drug causing the interaction, or the drug affected by the interaction. Alternatives might be to decrease the dose, or change time of administration.
2. Review all drugs in the active profile for appropriate indications and target a lowest effective dose.
3. Consider substitution of the suspected drug with another drug of similar efficacy but lower potential for interactions.
4. Order monitoring of drug concentrations where possible, at a frequency based on known pharmacokinetics.
5. Be prepared to discontinue drugs rather than add new ones.
6. Prescribe drugs on a regular basis with hold parameters instead of as needed.
7. Once an optimum drug profile is selected, observe the patient long enough for equilibration to be reached.
8. Document and communicate to other health professionals the management of the drug interaction to enhance continuity of care.

Panel 5: Team approach to the prevention of drug interactions in elderly people

Physician
- Clarify all medical disorders and establish appropriate drug choices in conjunction with the pharmacist.
- Regularly review the need for chronic drugs and discontinue unnecessary medications.
- Integrate information from the team and formulate a general care plan.
- Provide information on alcohol use.
- Document drug additions and discontinuations.
- When adding a new drug, screen for potential drug interactions.
- Try to avoid new prescription of a drug with a narrow therapeutic index when equally effective alternatives are available.
- Adjust dose or dose interval.
- Integrate a close monitoring plan when a drug-drug interaction cannot be avoided.
- Order appropriate periodic drug monitoring and follow-up.

Nurse
- Assess activities of daily living.
- Assess nutritional status.
- Provide mouth, dental, and bowel hygiene (for expert to monitor for anticholinergic side-effects).
- Document and report any falls, bleeding, acute changes in patient’s status, side-effects, etc.
- Assess and monitor drug administration and compliance.

Pharmacist
- Develop a therapeutic relationship with the patient and caregiver to assess attitudes, preferences, and drug compliance.
- Document a complete up-to-date drug history, including of-the-counter medications, health supplements, alcohol, and vitamins.
- Review medications for actual drug interactions; screen for drug–disease interactions and for drugs that are metabolised primarily via cytochrome P450 isoenzymes.
- Detect and document actual drug interactions in health record with action plan and follow-up; suggest drugs with a lower risk of interactions according to the patient’s drug profile.
- Monitor for adverse outcomes from potential drug interactions.
- Educate the patient and caregiver on non-prescription drug use, nutritional supplements, and potential drug-food interactions.
- Educate members of the health-care team on drug interactions.
- Document and report any adverse drug event.
- Reconcile active drug lists and pharmaceutical care plan on transition between care settings, to promote continuity of care.


detected by submission of drug lists to computer-assisted analysis. Methods such as computerised physician order entry (CPOE), computerised drug interaction software, and computerised decision support systems (CDSS) that detect and alert the physician and pharmacist to potentially serious outcomes can decrease the risk of drug errors.66–69 However, additional work needs to be done before CPOE and clinical information systems that are hospital based fulfill their potential for reliably preventing adverse drug interactions.

Large, commercial clinical information systems usually subscribe to standard drug knowledge systems such as the databases available from First Databank, Medi-span from Wolters-Kluwer Health, and Lexi-comp from Cerner, which are updated frequently. In the primary care office practice, the trend has been to use handheld computers or personal digital assistants for their mobility, robustness, simplicity of use, and low needs for technical support. Several reports have reviewed drug information and interaction software available for personal digital assistants.60–63 These studies emphasised the variability in quality and clinical applicability. Although there was no clear winner, the products from Lexi-comp—Lexi-Drugs and Lexi-Interact—were rated favourably.

The greatest effect is achieved by systems that proactively screen for interactions at the time of electronic prescribing. Alerts are displayed before an order is finalised, and changes can be made. Whatever electronic method clinicians choose, its value is most apparent when it is used consistently and continuously.44 Another key feature in the successful uptake of these systems is the avoidance of alert fatigue through careful system design and clinical validation of alerts to be displayed, along with intelligent recommendations.

Despite the use of computerised databases and software, there are substantial drawbacks. The databases must be kept up to date to show the constant influx of new information. Users have to filter the alert messages generated to identify those that are clinically significant. Cavuto and colleagues65 reported that pharmacists frequently over-rode computerised drug interaction alerts and filled the prescriptions that triggered alerts. The context and clinical significance of those interactions and the absence of feasible alternatives might have affected decisions. Finally, none of the commercial systems is designed for specific use in elderly patients, and analyses beyond simple drug–drug interactions, if available (ie, with computerised decision support systems), are cumbersome.
Development of the next generation of such systems, which addresses the above concerns, might potentially be useful as a means of managing drug interactions in elderly patients.

**How can clinicians help to decrease drug interactions in elderly people?**

With the knowledge that elderly people have several risk factors for drug interactions, the astute clinician can screen any specific situation to detect drug interactions. Asking the right questions frequently yields pertinent information that can help uncover a potential drug interaction. Panel 3 lists some helpful questions. Textbooks, software for personal digital assistants, and websites are available to help clinicians detect common drug interactions. Panel 4 shows actions that clinicians can take. In some cases the patient needs to be admitted for management and close monitoring. Recording an admission diagnosis as drug effect or drug interaction would help clarify the scope of this problem in elderly patients.

Results from a meta-analysis showed that elderly patients usually do better when their care is managed by a multidisciplinary team that practises the principles of geriatric care. The optimum drug management team should consist of a physician (geriatrician), nurse, and pharmacist. Communication between these professionals is crucial for success. By combining their knowledge and skills, a comprehensive plan can be developed and communicated to all care providers to enable best pharmacotherapy while the risks of drug interactions are reduced. Panel 5 outlines the respective contributions of all professionals.

**Conclusions**

Optimising drug treatment in elderly people is a real challenge. Modern drug development has produced a myriad of molecules, and elderly patients often take many drugs to treat several diseases. However, one challenge in the real world use of drug therapy is to identify, manage, and prevent drug interactions that can potentially negate the beneficial effects of drugs. Computer-assisted drug interaction software can serve as a reference source, but any generated recommendations have to be tempered by a holistic, geriatric, multiprofessional approach that is team-based. As the above strategies are implemented, appropriate pharmacotherapy in elderly people could result in better health and wellbeing for the patient and decreased health-care costs.

**Conflict of interest statement**

We declare that we have no conflict of interest.

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