Feature

MINIMISING THE RISKS OF POLYPHARMACY

Barbara Jesson looks at how ageing can affect the benefits of medication and the ways in which treatment can be improved

Summary

Polypharmacy holds particular risks for the older population, which nurses are in a good position to recognise and minimise. The aim of this article is to highlight the reasons why polypharmacy presents such a risk to older people and to consider what actions can be taken to address this problem.

Keywords
Adverse drug reactions, medication review, polypharmacy

CLINICAL EXPERIENCE indicates that older people now take an increased number of medications compared with ten or 15 years ago. It is estimated that 5 per cent of all hospital admissions in older people are caused as a result of adverse drug reactions (Cunningham et al 1997). The majority of drug-related hospital admissions are caused by antiplatelet agents, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs) or anticoagulants (Howard et al 2006). The growth in prescribing is partly a result of recent evidence about which drugs are effective in long-term conditions such as coronary heart disease (CHD) and diabetes. Often each of these conditions is not treated with just one drug but several different drugs, each having a different but synergistic action aimed at improving outcomes. Many older people have multiple comorbidities and consequently are prescribed an increasing range of medications.

The complexity of medication regimens can result in more adverse effects from medications, increased risk of interactions between different drugs and the potential for medicines for one disease to have an adverse effect on another disease. In addition, age-related physiological changes result in an increased risk of adverse effects.

Garfinkel and Mangin (2010) found that it is possible to halve the number of medicines prescribed to older people without significant adverse effect. Their results also showed that 88 per cent of participants reported an overall global improvement in health.

Pharmacological processes

To appreciate the complexity of polypharmacy risks, it is necessary to understand the pharmacological processes involved, how ageing affects these processes and why there is an increased risk.

Pharmacokinetics and pharmacodynamics are most relevant to the issue of ageing and polypharmacy. Pharmacokinetics can be described as ‘what the body does to the drug’. This is the journey of the drug into, through and out of the body, that is, how it enters the body (absorption), where it goes in the body (drug distribution), what happens to it in the body (metabolism) and how it is removed (excretion). Pharmacodynamics can be described as ‘what the drug does to the body’, that is, the drug’s action on the body’s receptors and biochemical processes.

Pharmacokinetics
Absorption
As people age, gastric secretions and motility reduce and intestinal surface area is decreased. Antacids are often taken by older people and can reduce the absorption of drugs, for instance angiotensin-converting enzyme inhibitors such as enalapril. Some antibacterials and drugs used in CHD such as digoxin or dipyridamole can also be affected. In practice, effects caused by changes in
drug absorption are not usually clinically significant except when drugs which decrease gastric emptying are also given, for example, antimuscarinics such as oxybutynin or opiates. Delays in gastric emptying can result in prolonged contact between a drug and mucosal surfaces, resulting in a higher risk of ulceration from drugs such as NSAIDs (Kelly 2001).

**Drug distribution** Several factors affect drug distribution in the body: blood flow to the tissues, lipid (fat) solubility of the drug and plasma protein binding. Older people generally have poorer blood flow to tissues which can result in a lower response to drug therapy, although this does not necessarily correspond to a reduced incidence of side effects.

Decrease in muscle and organ mass as a result of ageing leads to a proportional increase in fat, from 18 to 36 per cent in men and 48 per cent in women (Hudson and Boyter 1997). This increase in the proportion of fat alters the volume of distribution for lipid-soluble drugs, for example, diazepam, resulting in them being drawn out of the plasma into fatty tissue thereby remaining in the body for a longer time. Lipid-soluble drugs also enter the central nervous system (CNS) by crossing the blood-brain barrier with higher risks of falls and confusion.

Older people also have reduced total body water, thus decreasing the volume of distribution for water-soluble drugs such as digoxin and cimetidine. This can result in an increased concentration of these drugs and reduced doses are required to avoid adverse effects. Use of diuretics can exacerbate this problem.

Production of albumin (plasma protein) in the liver declines as the body ages, which affects drugs highly bound to plasma protein. Most drugs are bound to plasma to some extent, with only the part that is unbound available to act on a receptor - a site on the surface of a cell which binds with the drug to produce an effect, or which blocks the effect of another chemical. The effect of lower plasma protein levels (albumin) is to increase the concentration of free (active) drug in the body, so doses may need to be reduced as the person ages.

Problems can also occur with drugs that are highly bound when another, competing, drug is started displacing the original drug from its bound, inactive state and freeing it up to become active. An example is warfarin, which is displaced from its protein binding site by aspirin (Graham-Smith and Aronson 2002). In practice this does not mean that competing (interacting) drugs cannot be given, but it does require careful monitoring to avoid adverse effects. As the number of drugs increases, the potential for this to happen will also increase.

**Metabolism** The rate of elimination (metabolism and excretion) of a drug is described by its half life. The half life of a drug is a constant for any one person at any one time. It is the time taken for the plasma concentration of the drug to reduce to half its original value. Most drugs are metabolised in the liver by enzymes, which either break the drug down or combine the drug with other chemicals to make them pharmacologically inactive. Sometimes the metabolites, produced through the initial metabolic process, are themselves active and this will increase the duration of action because they will have to be broken down further to make them inactive.

The half life of a drug is often higher in older people: those of particular concern include glibenclamide, an oral hypoglycaemic; benzodiazepines, especially those that are longer acting such as diazepam and nitrazepam and fluoxetine, an antidepressant. Dosages that may have been suitable when younger can gradually accumulate because the body is no longer dealing with the medication efficiently and they may eventually reach toxic levels. It is important to recognise this in older people as they are more susceptible to the adverse effects of drugs.

The effect of a long half life is important in terms of drugs with a narrow therapeutic index, that is, where the difference between the dose needed for a therapeutic effect and that which causes toxicity is small. Examples of these drugs include amiodarone, digoxin and warfarin. Although liver function may decline with age, liver disease usually has to be severe before having a significant clinical effect because hepatic reserve is large; however, it is difficult to predict how drugs may be affected by liver dysfunction. The synthesis of blood clotting factors can be affected, increasing sensitivity to oral anticoagulants such as warfarin.

Some drugs are dependent on adequate blood flow to the liver for metabolism, for example, simvastatin, propranolol and verapamil. Therefore, if cardiac output is reduced, for instance in heart failure or diabetes, the metabolism of those drugs will be reduced too, increasing the likelihood of adverse effects.

The liver is the site of metabolism for many drugs, which is of particular significance when starting or stopping a drug that alters liver enzymes (Seymour and Routledge 1998). Certain drugs increase the rate of enzyme synthesis, while others inhibit it. If a liver enzyme inducer is started then other drugs that are metabolised through the same pathway will be metabolised faster because of the increased enzyme activity. Doses of existing medication may have to be increased to maintain a therapeutic effect.
The main problems occur when an enzyme inducer is stopped because raised liver enzymes return to normal levels with the risk that remaining drugs are then at too high a dose.

Many people may consider St John’s Wort to be a herbal remedy, but it has some significant interactions because of its action as an enzyme inducer (Case study). Other enzyme inducers include barbiturates, carbamazepine and phenytoin. It is worth remembering that alcohol and smoking also act as enzyme inducers and if a heavy smoker or drinker suddenly stops it may have an effect on some medications.

Those drugs that act as enzyme inhibitors reduce the metabolism of other drugs, leading to raised plasma levels and increased risk of adverse side effects and toxicity. This is particularly important where drugs with a long half life or narrow therapeutic range are concerned. Table 1 shows examples of enzyme inhibitors and drugs that can be affected.

Excretion Removal of a drug or its metabolites from the body is usually via the kidneys, although other routes are bile, sweat, saliva, breast milk, lungs, genital secretions and tears. Removal via the kidneys is determined by three factors:
- Glomerular filtration.
- Passive tubular reabsorption.
- Active tubular reabsorption.

Glomerular filtration is the most important factor. All drugs are filtered through the glomerulus into the kidney tubule and the extent to which they are excreted is directly proportional to the glomerular filtration rate (GFR). The normal rate is 120ml/min but this will be less if there is impairment of kidney function or if blood flow to the kidneys is poor.

Renal function declines with age and the British National Formulary (2010) recommends that it is wise to assume at least mild impairment of renal function when prescribing for older people. The use of drugs in patients with reduced renal function may cause problems for the following reasons:
- Reduced renal excretion of a drug or its metabolites can cause toxicity through accumulation of the drug in the body.
- Severe renal impairment may result in increased sensitivity to some drugs even though elimination is unimpaired. An example of this is where disturbed electrolyte balance can increase the risk of hyperkalaemia when potassium-sparing diuretics are prescribed. There is also an increased risk of sodium retention and fluid overload with use of NSAIDs.

Some drugs such as loop diuretics rely on active secretion into the kidney tubules for their action. If there is a reduction in renal blood flow it can result in less drug reaching the renal blood vessels. In renal impairment levels of creatinine are raised and creatinine competes with the drug for active secretion, therefore larger doses of loop diuretics are likely to be required for an adequate response. Many drugs require a reduced dose if there is renal impairment (Ponitcelli and Graziani 2010). Renal function is measured either by creatinine clearance usually using the Cockcroft and Gault formula (Box 1, page 18) or as an estimated GFR (eGFR) using the modification of diet in renal disease (MDRD) formula (Box 2, page 18), which uses serum creatinine, age, sex and race. Hospitals now generally use the MDRD formula, but because it does not adjust for weight it can overestimate the GFR of underweight patients compared with the Cockcroft and Gault formula. For frail older patients the Cockcroft and Gault formula is preferred (Melloni et al 2008).

### Table 1 Enzyme inhibitors and drugs that can be affected

<table>
<thead>
<tr>
<th>Enzyme inhibitor</th>
<th>Drug(s) whose plasma concentration may be raised</th>
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<tr>
<td>Cimetidine</td>
<td>Amiodarone</td>
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<tr>
<td>Grapefruit juice</td>
<td>Simvastatin, calcium channel blockers, for example, nifedipine</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Quetiapine, valproate, zopiclone</td>
</tr>
<tr>
<td>Calcium channel blockers – diltiazem/verapamil</td>
<td>Tricyclic antidepressants, phenytoin, some statins</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Carbamazepine, some antipsychotics, some benzodiazepines</td>
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**Case study**

A patient stabilised on digoxin 62.5mcg daily starts taking St John’s Wort to counteract a low mood without informing her GP. After some time the dose of digoxin has to be increased because it is being metabolised faster. The patient then decides to stop taking St John’s Wort. However, the GP, unaware she was taking it continues to prescribe the increased dose of digoxin. Some weeks later the patient starts to feel dizzy and nauseous as a result of digoxin toxicity. She is prescribed prochlorperazine with the risk of extrapyramidal side effects such as confusion, constipation, respiratory depression, photosensitivity, postural hypotension, insomnia, agitation, cardiac disorders and dry mouth.
Feature

As the body ages so there are changes to receptor sensitivity and this can result in reduced effectiveness of the drug, or increased sensitivity leading to more side effects, drug/drug interactions or drug/disease interactions.

Drugs with antimuscarinic properties and those which act on the CNS are two of the main classes of drugs that cause problems because of increased receptor sensitivity in older people. Antimuscarinics act by blocking muscarinic acetylcholine receptors commonly causing confusion, blurred vision, constipation, urinary retention and dry mouth. Drugs with antimuscarinic effects include antipsychotics, tricyclic antidepressants, oxybutynin and tolterodine. Drugs that act on the CNS can cause confusion, drowsiness, postural sway and unsteadiness and will therefore also increase the risk of falls. Benzodiazepines, opiate analgesics and drugs for Parkinson’s disease are of particular concern.

There is a decrease in sensitivity of β-adrenoreceptors which can result in decreased action of β₂ agonists (drugs which bind to the β-adrenoreceptors on a cell thus triggering a response by the cell) and β blockers (adrenoreceptor antagonists which are a type of drug that does not cause a response itself but blocks or lessens an agonist-mediated response). β₁-adrenoreceptor agonists are used for respiratory disorders, for example, salbutamol and salmeterol. β-adrenoreceptor blocking drugs are used for hypertension or heart failure, for example, bisoprolol and carvedilol. Although decreased sensitivity is not usually clinically significant and older people are often prescribed these medications, it is important to ensure that whatever medication is prescribed, it is continuously monitored for therapeutic effect as well as adverse effects otherwise ineffective drugs will continue to be prescribed. The co-prescribing of β₂-adrenoreceptor agonists and β-adrenoreceptor blocking drugs is contraindicated as it would result in one blocking the action of the other, thus worsening respiratory problems.

Homeostatic mechanisms become less responsive as people age, so the body is less able to adapt resulting in:

- Increase in postural sway, which may precipitate falls.
- Impaired reflex tachycardia, which increases risk of drug-induced hypotension.
- Increased risk of fluid and electrolyte imbalance especially with diuretics.
- Increased risk of hypothermia especially with antipsychotics.

Box 1: Cockcroft and Gault formula

<table>
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<tr>
<th>The estimated creatinine clearance in mL/min =</th>
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<tr>
<td>[(140 – age in years) x Weight in kg x Constant]</td>
</tr>
<tr>
<td>Serum creatinine</td>
</tr>
<tr>
<td>Constant = 1.23 for men, 1.04 for women</td>
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</table>

(British National Formulary 2010)

Box 2: Modification of diet in renal disease (MDRD) formula

<table>
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<th>Glomerular filtration rate (GFR) =</th>
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<tr>
<td>1.86 x (serum creatinine)⁻¹.₁₅⁴ x (age)⁻².₀²₃ x (0.₇₄₂ if female) x (1.₂₁₀ if African American)</td>
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The GFR is expressed in mL/min/1.₇₃m²

(Melloni et al 2008)

Pharmacodynamics

One of the main ways that drugs act is through receptors which can either be stimulated or blocked. This action can be directly by the drug or through an intermediary chemical which is already present in the body, for example, histamine or acetylcholine.

Drugs are not completely specific in their actions and they may exert an effect on more than one type of receptor or in more than one tissue area, often leading to unwanted side effects. Antipsychotics are a good example because they act on many different receptors. The action on dopamine receptors is thought to be responsible for their effectiveness against psychoses, however they also have anticholinergic and anti-noradrenergic effects which can cause postural hypotension, sedation and confusion.

Some drugs may also affect excretion of other drugs, preventing removal from the body and potentially leading to toxic levels. Examples of common drugs that have an effect on the excretion of others are:

- NSAIDs – such as ibuprofen – which reduce excretion of methotrexate.
- Diuretics which can cause lithium retention.
- Amiodarone which reduces excretion of digoxin.

Acute illnesses such as infections can cause dehydration and renal impairment potentially leading to drug toxicity. Some diseases such as diabetes and heart failure can affect drug excretion by worsening renal function or blood circulation which will lead to a reduction in blood flow to vital organs – such as kidneys or liver – and result in reduced metabolism or excretion.
Avoiding risks linked to polypharmacy

Nurses in the community and care homes are ideally placed to reduce the incidence and consequences of polypharmacy (Cowan et al 2002). As medicines have become more sophisticated, effective and commonplace, society has grown to believe that there is a ‘pill for every ill’ and if a prescription is not given we somehow feel cheated. However, to avoid the problems associated with polypharmacy, alternatives to medication should be considered where possible, for instance:

- Physiotherapy for osteoarthritis.
- Speech therapy for dysphagia.
- Dietary advice, such as increasing fluid intake and eating more high-fibre food and fresh fruit and vegetables.
- Sleep hygiene such as ensuring the room is a comfortable temperature and avoiding tea, coffee, alcohol and heavy meals before bedtime.
- Activities to relieve isolation and boredom such as reminiscing, gentle exercise and games.

Where medicines are required then they must be reviewed on a regular basis. However, there is a belief by patients that medication reviews and stopping medicine are cost-saving exercises and nurses need to correct this perception. Any monetary savings should always be a secondary consideration; the main aims of reviews are to: reduce risk, improve outcome and boost quality of life. Every opportunity should be taken to discuss with older people and their relatives the risks and benefits of medicine and to consider if a medication review would be beneficial. As people age they become more reliant on others to observe changes and ill effects and to initiate medication review. Nurses are crucial to this process and whenever medicines are prescribed nurses should ensure that they know:

- The therapeutic aim of the medication and how this will be measured.
- When the outcome is to be reviewed.
- What adverse effects might be expected and their significance, and if any steps can be taken to reduce them.
- How the drug will be monitored, for example, through blood tests.

The BNF has useful information on prescribing in older people.

Clinical medication reviews

The National Service Framework for Older People (Department of Health 2001) called for regular six monthly medication reviews for those aged over 75 and taking four or more medications. This should be considered a minimum requirement. It should also be remembered that chronological age is not the same as physiological age and many patients under 75 will also benefit from regular reviews.

Reviews should be triggered sooner if drugs have been prescribed that are known to cause problems. A holistic review will consider the individual drugs and indications and the potential interactions between different drugs and between drug and other disease areas, as well as the risk/benefit for that individual. If possible medication reviews should be done in conjunction with patients or their carers.

An effective medication review will include the following:

**The appropriateness of individual drugs:**

- What was the indication? Is it still necessary? Is a trial stoppage possible? Is there a non-medical alternative?
- Is the dose appropriate? Could it be reduced? Is it subtherapeutic?
- Efficacy: what is the evidence base? Is there a better and/or safer alternative?
- Is it being adequately monitored? For example, blood levels, urea and electrolytes and blood pressure.
- Is it being taken as intended? Up to 50 per cent of drugs are not taken as prescribed (National Institute for Health and Clinical Excellence (NICE) 2009).

**The appropriateness of each drug in relation to other drugs:**

- Adverse effects: is another drug prescribed for a possible side effect?
- Is there a possible interaction between different drugs?
- Has more than one drug been prescribed for the same condition? Can it be rationalised? For example, suboptimal doses of two laxatives or two analgesics.
- Are patients taking any ‘over the counter’ drugs or herbal remedies?

**Other medical conditions:**

- Could any of the drugs have an adverse effect on another condition?
- What level of renal impairment is there?
- Is there an alternative medicine which would benefit more than one condition?

**Drugs to avoid if possible (O’Mahony and Gallagher 2008). Consider if an alternative is available:**

- NSAIDs because of risk of gastric disturbance and effect on renal function.
- Long-acting oral hypoglycaemics because of risk of hypoglycaemic attacks.
- Antimuscarinics for Parkinson’s disease: increased risk of side effects, reduced effect of some Parkinson’s disease drugs.
- Benzodiazepines: risk of falls, confusion.
Feature

- Prochlorperazine: often inappropriately prescribed for dizziness.

**Drugs to review frequently. Consider if risk/benefit profile is still favourable:**
- All psychotropic medicines especially antipsychotics, tricyclic antidepressants and benzodiazepines.
- Antimuscarinics prescribed for urinary incontinence.
- Opioid analgesics, for example, codeine, dihydrocodeine.

**Medicine use reviews**

Once the drug regimen is correct, with a minimum number of essential medicines, it is important that they are taken as intended by the GP. Up to 50 per cent of people do not take their medicines correctly (NICE 2009). Many community pharmacists are now accredited to provide medicine use reviews (MURs) and this should be considered alongside the clinical review as an essential element of good care. MURs improve patients’ understanding of their medicines and devices and how to take them correctly. They also provide time to discuss any concerns the patient may have and to reinforce benefits, while ensuring that there are no adverse effects. If the patient is not compliant then there is an opportunity to discuss how to overcome barriers to taking medicines. The GP will be informed if there are any problems.

If the right drugs are being prescribed but they are not taken correctly, then not only will the patient be deprived of the full benefit of the treatment thus risking a poor outcome, but the chance of adverse effects will increase. In addition the GP, believing that the drugs are not working, might start to escalate treatment with higher potency drugs or higher doses being prescribed. MURs are particularly relevant when there has been a change in medication especially if this has occurred after a hospital admission.

**Conclusion**

Polypharmacy is an increasing problem and with advancing age the risk/benefit profile of many medications will change and may become less favourable. It is difficult to determine when the balance changes, but by being aware of the dangers, nurses will be able to improve patient outcomes (Jordan 2007).

Nurses should ensure that they are:
- Aware of what might precipitate adverse drug events, for example, acute illness, dehydration, chronic heart failure, new drugs and increased dosage.
- Familiar with the drugs that commonly cause problems.
- Alert to adverse effects including symptoms such as confusion, dizziness and constipation. Do not assume these are caused by ageing.
- Confident in their knowledge and raise concerns with prescribers.
- Realistic about what medicines can do – no medicine is completely safe.
- Able to educate patients, relatives and carers about risks.
- Familiar with alternative solutions to medication. By working effectively together with patients and other healthcare professionals, nurses can make a substantial contribution to improving outcomes for older people.

**References**


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