Polypharmacy – good or bad

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Polypharmacy is usually defined as the use of five or more drugs, including prescribed, over-the-counter, and complementary medicines. (1) Polypharmacy is also known as the use of multiple medications and is usually seen as a negative situation where an individual patient may be taking one or many more unnecessary medications among the group of appropriate medications. Polypharmacy is not a clinically useful independent marker of the quality use of medicines, as the type and dose of medications rather than the number of medications determine meaningful clinical outcomes.(2) This article examines some appropriate cases of polypharmacy as well as highlighting potential problem areas.

Polypharmacy can lead to adverse reactions and drug interactions, hospitalisations and other adverse outcomes (3). It is more common in older persons usually due to the larger number of medications that these people are taking and is increasing as Australians are living longer.

A summary from Australia’s Health 2010 (4) shows that:

- Cancer is Australia’s leading broad cause of disease burden (19% of the total), followed by cardiovascular disease (16%) and mental disorders (13%).
- The rate of heart attacks continues to fall, and survival from them continues to improve.
- Around 1 in 5 Australians aged 16–85 years has a mental disorder at some time in a 12-month period, including 1 in 4 of those aged 16–24 years.
- The burden of Type 2 diabetes is increasing and it is expected to become the leading cause of disease burden by 2023.
- The incidence of treated end-stage kidney disease is increasing, with diabetes as the main cause.
- Australia’s level of smoking continues to fall and is among the lowest for OECD countries, with a daily smoking rate of about 1 in 6 adults in 2007 but three in 5 adults (61%) were either overweight or obese in 2007–08.

Australia’s life expectancy at birth is among the highest in the world—almost 84 years for females and 79 years for males. Death rates are falling for many of our major health problems such as cancer, cardiovascular disease, chronic obstructive pulmonary disease, asthma and injuries but with this comes an increase in co-morbidities and the number of medications required leading to polypharmacy.

Extent of Medication Use

Community use:
A South Australian study carried out in 2004 of over 3000 participants showed that 48% of those over 75 years of age were taking more than four medications with almost 3% taking more than ten separate drugs. (5) In most medication use surveys studies relay on self-reported use which is often lower than actual use. A number of studies have shown that patients referred to pharmacists for home medicines review take an average of nine drugs. (6-9)
Factors associated with multiple drug use are increasing age, female gender, number of diagnoses, recent hospitalisation and depression. (10) Older patients are also significant users of complementary and alternative medicines (CAM). Although fewer Australians over the age of 65 years use CAMs compared with younger adults, among those with a chronic illness as many as 41% used at least one non-medically prescribed CAM and some used several. (11, 12) Vitamins and minerals are the most commonly used CAM (up to 35% of patients), while herbal or natural medicines were used by up to 14% of men and 23% of women. CAM use may contribute to polypharmacy and increase the risk of adverse drug reactions (ADRs) and interactions.

Preliminary results from a recent Australian mail survey showed that antihypertensives and simple analgesics/antipyretics were the most commonly used classes of conventional medicines. The most common conventional medicines were paracetamol, aspirin, and atorvastatin. Fish oils and glucosamine were the most common CAMs. Doctors recommended 81% of conventional medicines, whereas CAMs were recommended by doctors in 32% of cases and through the media in 17%. (13)

**Aged Care Facilities**

Studies at the commencement of Residential Medication Management Reviews (RMMRs) showed that with each resident prescribed an average of seven drugs (range 0–22). (14,15) A West Australian Nursing Home study identified polypharmacy in 91.2% of residents who were taking an average 9.75 medications per person. One third were prescribed an antipsychotic medication; and over 50% were found to be taking at least one potentially inappropriate medication. The combination of antipsychotics and antidepressants was the most frequently observed drug-drug interaction, being prescribed to nearly 16% of participants. (16) Non-drug strategies are preferable where possible.

A recent study of older adults in Supported Residential Services show a high prevalence of medication use and medication related risk factors but low awareness of Medication reviews. (17)

**Risks of adverse drug events**

Polypharmacy increases the risk of adverse drug events such as falls, confusion and functional decline. Medicines causing postural hypotension, balance disorders, cardiovascular insufficiency, blurred vision or confusion have been linked with an increased risk of falling (18). In addition changes in physiology, social and physical circumstances contribute to the risk of adverse drugs events. Older people are more likely to experience poor vision, hearing and memory loss, and have altered metabolic rates such as declining liver and renal function (18). Adverse reactions often go undetected or alternatively are misinterpreted as a medical condition and additional drugs are prescribed. Medicines classically highlighted in polypharmacy reviews as unnecessary include anticholinergic agents, excessive use of tranquillisers and psychotropic agents, medicines used to treat adverse effects of other medicines plus over-the-counter and complementary medicines.

Multiple prescribers also can contribute to polypharmacy. Home Medication and Residential Reviews carried out by pharmacists, on request from a general practitioner have been shown to significantly reduce the number of medications unnecessarily used (6, 7, 15).

Table 1 lists some ideas to manage for pharmacists to assist in the management of polypharmacy.
Table 1: Steps for managing and reducing inappropriate polypharmacy

<table>
<thead>
<tr>
<th>Steps</th>
<th>Action</th>
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| Prevention-reduction of medication | • Assess need for each medication, regular and ‘when needed’ medications.  
• Limit use of non-prescribed medications without evidence of efficacy in the patient.  
• Encourage patient to discuss ceasing unnecessary medications with prescriber e.g. using non-drug strategies instead of sleeping tablets [NB Ensure dose is weaned slowly to avoid adverse drug withdrawal symptoms]  
• Offer patients access to disease state information plus Consumers Medicine Information (CMI) |
| Regular medication review           | • Ensure an accurate drug history by examining medications actually taken in the home or Aged Care Facility  
• Check all medications prescribed and non-prescribed, for adverse effects, drug interactions, appropriate dosage, generic duplication, contraindications, administration difficulties, expiry, storage etc.  
• Match indication of drug with disease state and query unnecessary medications  
• Check ADEs are not being treated with additional medications  
• Ensure regular monitoring and review |
| Check and encourage adherence of essential medications | • Identify issues leading to possible non-adherence e.g., lack of knowledge, cost issues, which may lead to polypharmacy as the prescriber may not appreciate lack of adherence and prescribe an additional drug to treat the condition |
| Advocate effective prescribing      | • Apply discretion in the use of necessary and unnecessary medications  
• Consider recommendations to cease medications when patient’s goals of treatment are no longer attainable, or the condition has resolved.  
• Use an evidence guideline-based approach when offering recommendations to prescribers.  
• Work with prescribers, patients, family and patient advocates to prioritise medicines and discontinue others. |
| Minimise risk in duplication of prescribing | • Encourage patient to use a regular pharmacy and general practitioner  
• Encourage patients to have an up to date list of medications with them at all times |
| Use non-drug approaches             | • Encourage non-drug strategies to assist Chronic Disease Management.                                                                                                                                   |
| Communication                       | • Communication between patient, carer, prescriber (s), specialist and other health professionals as appropriate.  
• Check communication between multiple prescribers.  
• Ensure medication chart from hospital on discharge is sent to general practitioner, aged care facility and pharmacy where appropriate |
| Simplify regimen                    | • Aim for once or twice daily regimens where possible.  
• Minimise number of doses, dose times per day, and types of dose forms e.g. use the same type of asthma/COPD devices where possible |
Chronic disease management consists of medications but also of patient self-management where dietary changes, smoking and alcohol reduction, exercise and weight may reduce unnecessary use of medications.

Table 2 lists some commonly prescribed drugs, with monitoring frequently done and additional monitoring to detect adverse effects many of which may lead to additional drugs being prescribed (2). Table 3 provides some opportunities for reduction of polypharmacy using a systematic approach.

**Table 2: Commonly prescribed drugs and monitoring** (adapted from 3)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequently monitored effects</th>
<th>Effects not frequently monitored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin Converting Enzyme inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs)</td>
<td>Blood pressure</td>
<td>Renal function, cough</td>
</tr>
<tr>
<td>Aspirin (low dose)</td>
<td>Cardio and cerebrovascular events</td>
<td>Gastrointestinal effects, bruising</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Bone mineral density</td>
<td>Gastrointestinal reflux symptoms, dental healing</td>
</tr>
<tr>
<td>Betablockers</td>
<td>Angina, blood pressure</td>
<td>Changes in blood glucose levels, tiredness</td>
</tr>
<tr>
<td>Corticosteroids (inhaled)</td>
<td>Asthma exacerbations</td>
<td>Thrush, dysphonia, decreased bone mineral density, mood changes</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Serum concentration</td>
<td>Anorexia, nausea, slow pulse</td>
</tr>
<tr>
<td>Diltiazem, verapamil</td>
<td>Blood pressure</td>
<td>Constipation, bradycardia</td>
</tr>
<tr>
<td>Iron</td>
<td>Iron studies</td>
<td>Constipation</td>
</tr>
<tr>
<td>NSAIDs, COX-2s</td>
<td>Pain relief</td>
<td>Blood pressure, renal function, fluid retention, gastrointestinal. Respiratory adverse effects</td>
</tr>
<tr>
<td>Metoclopramide, prochlorperazine</td>
<td>Nausea,</td>
<td>Extrapyrimidal effects, drowsiness</td>
</tr>
<tr>
<td>Nitrates</td>
<td>Angina frequency</td>
<td>Postural hypotension</td>
</tr>
<tr>
<td>Opioids</td>
<td>Pain relief</td>
<td>Constipation, confusion</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors (SSRIs)</td>
<td>Depression</td>
<td>Hyponatraemia, sexual dysfunction, gastrointestinal bleeding, postural hypotension</td>
</tr>
<tr>
<td>Statins</td>
<td>Cholesterol</td>
<td>LFTs, creatinine kinase</td>
</tr>
<tr>
<td>Thiazides</td>
<td>Blood pressure</td>
<td>Postural hypotension, incontinence, metabolic disturbances</td>
</tr>
</tbody>
</table>
Table 3: Opportunities for reduction of polypharmacy (adapted from 19,20)

<table>
<thead>
<tr>
<th>Reason for action</th>
<th>Example</th>
</tr>
</thead>
</table>
| Possible medication error or adverse effect | • Taking two therapeutically equivalent versions of a single drug ie generic duplication  
                                 • Taking drug with little therapeutic benefit e.g. dextropropoxyphene.  
                                 • Adverse drug event or side effect  
                                 • Drug interaction of significance e.g. ACEI, diuretic and NSAID (‘triple whammy’) |
| Simplification of regimen                | • Combine thiazide diuretic and antihypertensive with combination product; or other combination antihypertensive agents  
                                 • Use SR form instead of three times a day dosage |
| Clinical benefit unlikely                | • Use of multivitamins with adequate diet  
                                 • Use of complementary medicines without evidence |
| Regular use can be reduced to as needed  | • Seasonal allergies e.g. use of antihistamines, inhaled corticosteroids  
                                 • Use of PPIs for reflux only if dietary indiscretion  
                                 • Use of NSAIDs or COX 2 inhibitors for arthritis  
                                 • Analgesics, benzodiazepines, sedatives |
| Benefit is likely to have been achieved  | • Depression resolved after at least 12 months treatment  
                                 • Hormone replacement therapy after 5 years |
| Drug use has resulted in no change of condition | • Use of cholinesterase inhibitors for dementia  
                                 • Use of anticholinergic drugs for continence |
| Non drug intervention                    | • Diet and exercise e.g. statins, hypoglycaemics, antihypertensive  
                                 • Cognitive behavioural therapy  
                                 • Diversional therapy to replace antipsychotics, anxiolytics and benzodiazepines for behavioural disturbances |
| Benefit is unlikely to be realised       | • Long-term use of bisphosphonates with reduced life expectancy |
| Prioritisation                           | • Multiple medicines, confused, falls risk, cost, patient complains of too many medicines |

Table 4 provides a list of medicines which are generally not advised to be used in older people and are a target for deprescribing. Screening tools for Inappropriate Prescribing (IP) have been devised, principally by Beers’ Criteria and the Inappropriate Prescribing in the Elderly Tool (IPET) (21,22). Although Beers’ Criteria have become the most widely cited IP criteria in the literature they have deficiencies, including several drugs that are rarely prescribed nowadays. Based on Australian data, Basger, Chen & Moles have identified 48 prescribing indicators which may assist rational prescribing. (23) Deprescribing is an important aspect of Medication reviews, but there are many barriers to actually ceasing
medications particularly the patient! Care needs to be taken when medicines are ceased to ensure safety and minimise adverse withdrawal effects. Table 5 summarises drugs requiring caution when ceased.

### Table 4: Medications generally considered inappropriate in older persons (24 -28)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Inappropriate for</th>
</tr>
</thead>
<tbody>
<tr>
<td>amantadine</td>
<td>indomethacin</td>
</tr>
<tr>
<td>amtriptyline</td>
<td>methylidopa</td>
</tr>
<tr>
<td>benzhexol</td>
<td>metoclopramide</td>
</tr>
<tr>
<td>benztropine</td>
<td>nitrazepam</td>
</tr>
<tr>
<td>chlorpromazine</td>
<td>nitrofurantoin</td>
</tr>
<tr>
<td>cimetidine</td>
<td>NSAI Ds</td>
</tr>
<tr>
<td>dextropropoxyphene</td>
<td>oxybutynin</td>
</tr>
<tr>
<td>diazepam</td>
<td>prazosin</td>
</tr>
<tr>
<td>dothiepin</td>
<td>prochlorperazine</td>
</tr>
<tr>
<td>doxepin</td>
<td>propantheline</td>
</tr>
<tr>
<td>flunitrazepam</td>
<td>psychotropic drugs</td>
</tr>
<tr>
<td>glibenclamide</td>
<td>theophylline</td>
</tr>
<tr>
<td>glimepramide</td>
<td>thioridazine</td>
</tr>
<tr>
<td>hydrochlorothiazide 50mg</td>
<td>trimethoprim-sulfamethoxazole</td>
</tr>
</tbody>
</table>

*In some situations some of the above medications may be appropriate with a risk versus benefit assessment

### Table 5: Drugs requiring caution when deprescribing (Adapted from 29)

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Adverse drug withdrawal effect</th>
<th>Suggested withdrawal protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Withdrawal effects e.g. delirium, insomnia, seizures</td>
<td>Wean very gradually. May require detox program</td>
</tr>
<tr>
<td>Alphablockers</td>
<td>Rebound hypertension, agitation with sudden cessation</td>
<td>Wean gradually watch for symptoms</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Anxiety, nausea, vomiting, headache, dizziness</td>
<td>Wean gradually especially after long term use</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Dysphoric mood, agitation, headache</td>
<td>Wean gradually watch change over times</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Dyskinesia, nausea, vomiting, headache</td>
<td>Wean gradually especially clozapine</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Withdrawal effects e.g. delirium, insomnia, seizures</td>
<td>Wean very gradually especially in long term or high dose, May need to use LA agent for weaning</td>
</tr>
<tr>
<td>Betablockers</td>
<td>Rebound tachycardia, palpitations, reemergence of angina</td>
<td>Wean gradually watch for symptoms</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>HPA suppression, re-emergence of inflammatory conditions</td>
<td>Gradual weaning after long term use, monitor for symptoms</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Re-emergence of AF</td>
<td>Caution of history of AF</td>
</tr>
<tr>
<td>Frusemide</td>
<td>Re-emergence of heart failure, oedema</td>
<td>Caution if CCF, observe for symptoms</td>
</tr>
<tr>
<td>Nitrites</td>
<td>Re-emergence of angina</td>
<td>Gradual tapering</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>Withdrawal effects e.g. delirium, insomnia, seizures</td>
<td>May require detox program</td>
</tr>
</tbody>
</table>
Polypharmacy may be unavoidable, given that multiple drug therapy has become the standard of care in most chronic conditions. Current guidelines recommend that patients with ischaemic heart disease, heart failure, or diabetes should be assessed for an antiplatelet agent, statin, ACE inhibitor, and other antihypertensives as well as agents specific to their primary condition. Polypharmacy is inevitable when treating a common chronic condition such as diabetes where tight cardiovascular control is necessary as well as hypoglycaemic agents. In addition patients with cardiovascular conditions may also require treatment other co-morbidities such as osteoporosis adding additional therapeutic agents e.g. bisphosphonate, or selective oestrogen receptor modulator, strontium then calcium and vitamin D supplementation. Hence the issue is not how to reduce polypharmacy, but how to reduce unnecessary polypharmacy (3).

Evidence is now available showing that older patients may be under-prescribed useful drugs, including aspirin for secondary prevention in high-risk patients; beta blockers, antiplatelet or anticoagulant agents and a statin following myocardial infarction; ACEIs or ARBs for patients with type 2 diabetes, hypertension and proteinuria; ACEIs or ARBs for patients with systolic heart failure, and warfarin for nonvalvular atrial fibrillation (24). The benefits of warfarin are greatest in older persons but so are the risks of adverse outcomes and difficulties of anticoagulant management particularly when polypharmacy issues are prevalent (25). Dabigatran (Pradaxa) approved for AF but not yet PBS for this indication, requires less monitoring but is contraindicated if renal clearance<30mL/min.(24)

Whilst there are many concerns about polypharmacy many of these issues involve a broader range of drug-related problems that need to be addressed (10). Setting of therapeutic goals for individual patients, deciding on the appropriate therapeutic approach drug and non-drug, close monitoring for effectiveness and adverse effects will assist in rational prescribing to find the balance between too few and too many drugs for the aging population. For many common conditions therapy discontinuation may be appropriate after a specified period but patients’ values and preferences are important to consider. Using a model of shared decision-making and communication is most likely to provide optimum results.

Questions

1 All the following statements are true, except for:
   a) Cardiovascular disease is Australia’s leading broad cause of disease burden, followed by cancer and mental disorders.
   b) The rate of heart attacks continues to fall, and survival from them continues to improve.
   c) Around 1 in 5 Australians aged 16–85 years has a mental disorder at some time in a 12-month period, including 1 in 4 of those aged 16–24 years.
   d) The burden of Type 2 diabetes is increasing and it is expected to become the leading cause of disease burden by 2023.
   e) The incidence of treated end-stage kidney disease is increasing, with diabetes as the main cause.

2 All the following statements are true, except for:
   a) Polypharmacy usually involves people taking four or more drugs per day and may be good.
   b) Polypharmacy is always inappropriate.
   c) Polypharmacy can lead to adverse events such as falls, confusion and functional decline.
   d) Patients may be reluctant to cease medications.
   e) Polypharmacy may include drugs used to treat side effects of other drugs
3 All the following statements are true, except for:
   a) Over 25 percent of people over 65 are likely to be using 6 or more medicines per day.
   b) Poor vision, hearing, memory loss are not related to adverse drug events.
   c) Anticholinergic agents, anxiolytic and complementary products may cause problems in people taking multiple medications.
   d) The use of antihypertensive, antilipidemic, and antihypoglycaemic agents are common causes of polypharmacy but may be rational.
   e) Multiple prescribers, including specialists, may contribute to polypharmacy.

4 All the following statements are true, except for:
   a) Check that generic medicines are not being duplicated.
   b) Check that side effects are not being treated with an additional medicine.
   c) Encourage patients to use a regular pharmacy and general practitioner.
   d) Aim for three to four times a day regimens to coincide with meals and going to bed to improve adherence.
   e) The use of combination products may improve adherence.

5 All the following statements are true, except for:
   a) People taking ACEI and ARB should have renal function monitored.
   b) People taking NSAIDs including COX-2 inhibitors should have renal function monitored and used only when necessary if possible.
   c) Hypernatraemia may be a problem for people taking SSRIs.
   d) Gastrointestinal bleeding may occur with patients taking SSRIs.
   e) ACEI or ARBs should be prescribed for people with type 2 diabetes and hypertension and macroalbuminuria or proteinuria.

References:

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19. Alexander GC, Maliha A, Sayla MA, Holly M, Holmes HM, Sachs GA Prioritizing and stopping prescription medicines CMAJ 2006; 174 (8); 1083-1084