

OCCURRENCE, COMPLICATIONS AND INTERVENTIONS OF POLYPHARMACY- A REVIEW

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ABSTRACT

In the past, when an apothecary individually compounded medications; Polypharmacy was referred to the mixing of many drugs in one prescription. Today Polypharmacy implies to the prescription of too many medications for an individual patient, with an associated higher risk of adverse drug reactions and interactions. Situations certainly exist where the use of multiple medications is justified in order to yield effective pharmacotherapy. Polypharmacy is a problem of substantial importance, in terms of both direct medication costs and indirect medication costs resulting from drug-related morbidity. Moreover it is a preventable problem. Available data suggests physicians and clinical pharmacists have the potential to have a large effect in combating this problem through a variety of interventions such as reducing the number of medications taken, reducing the number of doses taken, increasing patient adherence, preventing adverse drug reactions (ADRs), improving patient quality of life and decreasing facility and drug costs. In this article, we describe how Polypharmacy might occur and what complications cause, we review studies evaluating interventions to reduce unnecessary prescribing, and finally; we identify practical means for the busy physician to avoid this problem.

Keywords: Polypharmacy, Adverse drug reactions, Aged, Quality use of medicines, Clinical pharmacist.

INTRODUCTION

Although the term Polypharmacy has evolved over time and is often used to mean many different things in different situations, its basic definition is quite simple more drugs are prescribed or taken than are clinically appropriate¹. The specific number of drugs taken is not itself indicative of Polypharmacy as all of the drugs may be clinically necessary and appropriate for the patient; however, as the number of prescribed drugs increases, so do the chances of Polypharmacy². A 2002 US survey indicated that 25% of the overall population takes 5 or more medications per week³. When specifically considering the population 65 years of age and older, this percentage increases to about 50%, with 44% of men and 57% of women taking 5 or more medications per week and 12% of both sexes taking 10 or more prescriptions per week⁴. The most worrisome consequence of Polypharmacy is the occurrence of adverse drug reactions (ADRs), but increased drug costs and patient quality of life are also significant issues^{5,6}.

Due the fact that people are living longer, the elderly population, which often suffers from multiple chronic diseases requiring multiple medications, continues to increase. These patients are much more likely to experience Polypharmacy and its negative consequences, especially adverse drug reactions (ADRs)⁷⁻¹¹.

ADRs are one of the most troubling issues surrounding medication use in the elderly, as this patient population is more likely to have poor outcomes than others¹². They affect approximately 10-20% of hospitalized patients and around 7% of the general population; this number

increases when the population of interest is limited to the elderly¹³. Because the elderly are much more likely than other populations to have poor outcomes as a result of Polypharmacy due to their generally poorer overall health status, it is crucial to consider any intervention that has the potential to reduce this problem – a role that clinical pharmacists are well trained to fill¹⁴.

DEFINITIONS OF POLYPHARMACY

Although the term "Polypharmacy" is frequently used, it is not clearly defined in the literature. The definition of Polypharmacy is still controversial. However, it may be defined as the use of one medication to correct the adverse effect of another or the increase on the number of medications considering five or more associations¹⁵⁻¹⁷. One simple definition is based on the total number of different medications a patient takes concurrently¹⁸.

Topical and herbal medications are generally excluded of this definition as they are often not included in the traditional methods of assessing prescription quality. Vitamins and minerals taken on as needed basis are also generally excluded in these assessments because of the inconsistent inclusion of these medications in Polypharmacy.¹⁹

The duration of therapy has been another criterion described to define Polypharmacy. Veehof et al²⁰ defined a minimum period of 60 days. However, this criterion has not yet been validated.

The diagnostic of several concomitant conditions may lead to Polypharmacy. Considering the large number of Polypharmacy concepts, there is need of an agreement in



relation to this definition to evaluate its frequency, control its occurrence and to identify the risk of adverse reactions associated with Polypharmacy. There are several reasons for Polypharmacy:

1. As the population ages, Polypharmacy increases. The elderly often required multiple medications to treat multiple health-related conditions.²¹
2. Patient with multiple co-morbid medical conditions also required numerous medications to treat each condition. It is not unreasonable for patient with multiple co-morbid medical conditions to be on 6 to 9 medications to reduce his or her long term risk for those conditions, i.e, diabetes conditions and coronary events.²²
3. A recent hospitalization also puts patients at risk of Polypharmacy. Medicines are started and stopped quite frequently during patient hospital stay.
4. Multiple doctors are prescribing medications for the same patient. Once a patient starts a medication, it is never discontinued.
5. Lack of patient education is the most common reason. Doctors don't inform patients or patients do not ask questions.

Polypharmacy is associated with suboptimal prescribing. The more drugs a patient is exposed to, the more likely they are to be prescribed inappropriately. 'Potentially inappropriate medications' in the elderly include those with sedative or anticholinergic effects and long-acting non-steroidal anti-inflammatory drugs^{23, 24}. Polypharmacy may occur when additional drugs are prescribed to treat the adverse effects of other drugs. This is known as the 'prescribing cascade'. Other suboptimal prescribing associated with Polypharmacy includes prescription of more than one drug in the same class or prescription of a drug that interacts with or is contraindicated in combination with another of the patient's medicines²⁵. Ironically, in a study of older patients the probability of under-prescribing – defined as lack of an indicated drug when no reason could be found for not prescribing it – also increased significantly with the number of drugs prescribed.

Polypharmacy in of itself is not problematic. Consider, for instance, a patient with type 2 diabetes and existing coronary heart disease who has received a recent coronary stent for myocardial infarction. It is not unreasonable or uncommon for this patient to be on 6 to 9 medications to reduce his or her long term risk for diabetes complications and secondary coronary events²⁶. In fact, strict adherence to national treatment guidelines for this patient will result in a minimum of 6 concurrent prescription therapies^{27, 28}.

Polypharmacy can, however, become problematic when negative outcomes occur. Polypharmacy has been shown to result in:

1. Unnecessary and/or inappropriate medication prescribing.
2. Increased risk for drug interactions and adverse drug reactions²⁹.
3. Nonadherence.
4. Increased overall drug expenditures.

POLYPHARMACY: ASSOCIATION WITH ADVERSE PATIENT OUTCOMES

Polypharmacy is sometimes overlooked because the symptoms it causes can be confused with symptoms of normal aging or another disease. Sometime resulting in still more drugs being prescribed to tract the new symptoms. Some signs that are caused by interactions between drugs or side-effects of drugs can include:^{30, 31}

- Tiredness, sleepiness or decreased alertness.
- Constipation, diarrhea or incontinence.
- Loss of appetite.
- Confusion (all time or some time).
- Falls.
- Depression or lack of interest in usual activities.
- Weakness.
- Tremor.
- Hallucinations - Seeing or hearing things.
- Anxiety or excitability.
- Feeling dizzy.
- Decreased sexual behavior.
- Skin rashes.

TYPES OF POLYPHARMACY

Polypharmacy more commonly has a negative connotation, but sometime it is necessary and can be beneficial in treating certain medical conditions. Polypharmacy can be categorized into 2 major classes.^{33, 34}

1. Therapeutic Polypharmacy

This type occurs where multiple drug regimens are carefully monitored by clinicians and are necessary for the treatment of conditions and for achieving a therapeutic goal. An example of therapeutic Polypharmacy is the combination therapy of isoniazid, rifampin, ethambutol, pyrazinamide and pyridoxine in the initial treatment of tuberculosis. Another example of therapeutic Polypharmacy is the multiple agents used in the management of congestive heart failure such as digoxin, angiotensin- converting enzyme inhibitors and a diuretic³⁵. This example illustrates two prescribing principles:

- Using multiple drugs can help achieve an intended therapeutic goal.
- Adding one drug can prevent a known adverse effect of another drug.



Using combination drug therapy can also generate cost benefits such as by adding a drug to delay or inhibit the metabolism of an expensive principal drug.³⁶

2. Contra-therapeutic Polypharmacy

This type of Polypharmacy occurs where an individual experiences unanticipated or unintentional adverse effects while patient is on a drug regimen and is not monitored. For example contra-therapeutic Polypharmacy may occur when a patient is given the mood-stabilizing drugs valproate and carbamazepine (CBC) at the same time.³⁷ The combination may be dangerous in the following ways:

- Carbamazepine oxidized by arene oxidase to CBZ 10, 11-epoxide, which is hydrolyzed by epoxies hydrolase to CBZ 10, 11-dihydroxide. The metabolite CBZ 10, 11-epoxide has both therapeutic and toxic effects.³⁸
- In monotherapy, the rate of carbamazepine to CBZ 10, 11-epoxide is 10:1 with CBZ 10, 11-epoxide having a shorter half-life than carbamazepine.
- When carbamazepine and valproate are taken as co-pharmacy, valproate blocks the hydrolysis of CBZ 10, 11-epoxies by inhibiting epoxide hydrolase, so that the ratio of carbamazepine to CBZ 10, 11-epoxide becomes 2:1. Higher concentrations of the epoxide metabolite contribute to neurotoxicity.³⁹

CLASSES OF POLYPHARMACY^{40, 41}

Polypharmacy may be classified as:

1. Same-class Polypharmacy: The use of more than one medication from the same medication class (e.g. two selective serotonin reuptake inhibitors, such as fluoxetine plus paroxetine).⁴²

2. Multi-class Polypharmacy: The use of full therapeutic dose of more than one medication from different medication classes for the same symptom cluster (e.g. the use of lithium along with an atypical antipsychotic such as fluoxetine plus olanzapine).⁴³

3. Adjunctive Polypharmacy: The use of one medication to treat the side effects or secondary symptoms of another medication from a different medication class (e.g. use of trazadone along with bupropion for insomnia).

4. Augmentation: The use of medication at a lower than normal dose along with another medication from a different medication class at its full therapeutic dose, for the same symptom cluster (e.g. the addition of low dose of haloperidol in a patient with a partial response to risperidone).

5. Total Polypharmacy: The total count of medications used in a patient, or total drug load. Consideration of total Polypharmacy should include prescription medications, over-the-counter medications, alternative medical therapies, and elicit pharmacological agents.⁴⁴

EPIDEMIOLOGY OF POLYPHARMACY AND CLINICAL OUTCOMES

In a study comparing the 1980 and 2004 age group population pyramids, an increase was seen in the population older than 60 years; from 6.1% to 8.6%.⁴⁵ Due to an increased lifespan of the elderly both in developed and developing countries, identifying medication interactions aimed at preventing adverse drug reactions becomes paramount.⁴⁶ Proportionally, the elderly use more drugs compared to other age groups. Passarelli et. al⁴⁷ reported an average between 9.9 and 13.6 drugs in inpatients. The number of medications used in outpatient treatment was lower, ranging from 1.3 to 2.3 drug/patient.⁴⁸

A Brazilian study investigated 45 elderly and found that Polypharmacy in 33.3%. Antihypertensive agents were the most commonly used drugs, accounting for 53.3% of prescriptions.⁴⁹ A 32% prevalence was found for cardiovascular medications in another prospective study involving hospitalized or bedridden elderly patients. It was also observed that of those who took drugs with tea (57%), 12% did not believe tea could reduce the therapeutic efficiency.⁵⁰

Loyola et. al⁵¹ showed an association between the number of medical consultations and use of prescribed medications. Self-medication rate was lower among those who attended periodical medical consultations and high self-medication rates may be associated to lack of medical care. In contrast to studies conducted in developed countries, lower use of prescribed medications among elderly patients with lower socioeconomic condition was seen.⁵²

In one of the few prospective studies on Polypharmacy, Veehof et al followed up 1,544 elders for three years, and identified a 42% incidence rate of Polypharmacy. The number of medications used in the long term at the beginning of the cohort was the best predictor of Polypharmacy development. The incidence of arterial hypertension and atrial fibrillation was associated to significant increase in Polypharmacy (risk ratio of 37.3 and 19.6, respectively).⁵³

In regard to the incidence of Polypharmacy in outpatients, a study²⁵ found five chronic diseases on average per elderly, who took about 11 medications each. Also, it was found that 81% of them had prescriptions considered as inadequate, had inadequate treatment adherence or used drugs with narrow safety margin, which could cause medication toxicity.^{54, 55}

ECONOMIC IMPACT OF POLYPHARMACY

In Netherlands, there was a progressive increase in medication consumption among the elderly for 20 years (1989–08).⁵⁶ In the United States, the increase in medication expenditure from 1991 to 2000 was around 8.5%. Japan, on the other hand, had a disproportional growth with an estimated expenditure per elder in 1991 of US\$ 130 per capita.⁵⁷



An increased consumption of herbal remedies in this age group was also seen as they are sold over the counter, thus facilitating access to these drugs without requiring medical prescription. Herbal remedies are part of the so-called complementary therapy.⁵⁸ Three factors have been indicated as key for increased costs with medications in the elderly: increased use of prescribed medications, increased costs of prescription drugs and the advent of new drugs. This increased expenditure due to a greater number of prescribed drugs could be minimized by using less costly drugs.⁵⁹

The association between urinary incontinence, delirium and Polypharmacy is common in people older than 50 years.⁶⁰ Drugs used in the treatment of urinary incontinence are usually adrenergic, sometimes inducing delirium as an adverse effect. As it requires a different drug to reduce this adverse effect, this combination characterizes Polypharmacy. In turn, Polypharmacy itself may cause several complications, among them urinary incontinence and delirium.^{61, 62}

Other factors associated to Polypharmacy in the elderly include the number of serious diseases which require a higher number of medications for its treatment and incur in higher expenditure with physicians and clinical pharmacists as more providers will be involved.^{63, 64}

Admission rates may increase since increasing population age is associated to higher risk of side effects in the elderly, a condition that can be aggravated by the use of Polypharmacy.⁶⁵ The most commonly complications associated to adverse drug reactions include gastrointestinal complications, accounting for 19%, and metabolic and hemorrhagic complications. The most commonly drugs involved in these events are diuretics, calcium blockers (9%), digoxin (8%), and nonsteroidal anti-inflammatory agents (8%).⁶⁶ Adverse drug effects produced an increased rate of hospital admission in elderly patients of around 4% and 38 (4%) died due to adverse drug effects. For each drug used by the elder, there is a 65% increase in the likelihood of hospital admission due to adverse drug effects.⁶⁷

POLYPHARMACY CONTROL MEASUREMENTS

1. **Maintain an accurate medication and medical history:** Identify all medications, including any OTC therapies. Having a complete list of medications can deter a provider from adding on an additional therapy. Further, knowledge of a specific medication being used may explain a patient-specific symptom or complaint. For example, knowing a patient is on an opioid analgesic may explain why he or she has constipation.⁶⁸ A complete history of the patient's medical condition also is important. Identifying the patient medical history allows the pharmacist to identify inappropriately prescribed medications.⁶⁹ For instance, metformin is not appropriate for patients with end-stage kidney disease.

2. **Link each prescribed medication to a disease state:** each medication should match a patient's diagnosis. Any medication that does not match a diagnosis is potentially unnecessary, and an attempt to discontinue the medication should be made.⁷⁰

3. **Identify medications that are treating side effects:** The use of multiple medications leads to a higher risk of side effects. When side effects occur, additional medications can be initiated to treat the side effect. A common example includes the use of laxatives to treat the medication side effect of constipation.⁷¹ Other examples include:
 1. The use of sleeping meds to treat insomnia caused by theophylline, prednisone and antidepressants.⁷²
 2. Aricept (donepezil) to treat cognitive impairment caused by obybutynin, tolterodine, antihistamines, opioids and benzodiazepines.⁷³

Discontinuing one drug that is causing a side effect can often lead to the discontinuation of several drugs.

4. **Initiate intervention to ensure adherence:** Treatment adherence of the elderly patient is another factor that impairs Polypharmacy reduction. Medication adherence can be defined as consistency between medical prescription and drugs consumed by the patient.⁷⁴ Compliance is lower among elders older than 85 years compared to those aged from 60 to 74 years. Another factor that contributes to the reduction of drug bioavailability is the fact that older adults drink less water and tend to take their medication with food, and make use of drugs, such as tranquilizers and laxative agents, by themselves.⁷⁵ Using combination products (i.e., Lisinopril/hydrochloriazide combination pill) will reduce overall pill number and potentially improve adherence. Other strategies include using generic options to reduce cost and using adherence aids such as pillboxes.⁷⁶

Discontinuing one drug that is causing a side effect can often lead to the discontinuation of several drugs.

5. **Reconcile medications upon discharge from hospital or skilled nursing facility:** as mentioned above, a risk factor for Polypharmacy includes recent hospitalization. The transfer of a patient from a hospital to his or her home is associated with adverse events and negative outcomes, most of which are related to changes in the patients drug therapy during treatment in these facilities. Evaluating a patients medications regimen and educating a patient upon discharge from a facility is likely to reduce duplicate therapy, inappropriate prescribing, and reduce unnecessary medication.⁷⁷

6. **Prevention:** the appropriateness of the medication for the patient and the potential for side effects must be considered. Any drug that is unnecessary, inappropriate, or has a high likelihood for causing



side effects that would require additional therapy should be avoided.⁷⁸

ROLE OF PHYSICIAN AND CLINICAL PHARMACIST

Physician and clinical pharmacist play an important role in the reduction of Polypharmacy in the elderly. Physicians evaluate aspects concerning the use of adequate medications; reduction of medication doses without affecting treatment efficiency; adjustment of doses beyond the drug safety margin; and correct use of the medication by elderly patients.^{79, 80}

The role of a clinical pharmacist has been confirmed as vital in the development of recommendations for both physicians and patients. A prospective study has shown a reduction of 24% in the use of inappropriate drugs as well as significant reduction in adverse drug effects when compared to the control group.⁸¹

A physician practicing in Louisiana and specializing in adult medicine, surgery, nutrition, and critical care, has stated that pharmacists can aid in the reaction or avoidance of Polypharmacy in the following ways:⁸²

- Screening patient drug profile.
- Assessing the effects of comorbid conditions.
- Reviewing potential drug- drug interactions.

Some of the most common pharmacological agents that are associated with adverse effects are nonsteroidal anti-inflammatory drugs, psychotropic, antihypertensive, and antibiotics. One important step is to review and assess the specific indications for certain medications.⁸³

As stated above, it is very common, particularly in elderly, to see medications prescribed to treat side effects of other medications.⁸⁴ Clinical pharmacists can make recommendations to discontinue those medications and prescribe alternative therapeutic choices. As clinicians, pharmacists can play a fundamental role in identifying those agents that may not be necessary in a patient's drug regimen. They also may be able to suggest non-pharmacological therapies to meet a patient's particular needs.

Although the solution may not be a simple one, in most cases Polypharmacy can be managed through a multidisciplinary approach. The objective of appropriate pharmacological therapy is to treat or manage disease states, to prevent complications associated rich comorbidities, and to ease or eradicate pain.⁸⁵ The achievement of these goals can be obtained through precise and routine drug monitoring. Therefore, the ultimate challenge for all healthcare professionals is to ascertain the most suitable drug therapy for each patient that will enhance that patient's quality of life without compromising the patient's ability to function and put him or her at risk for adverse reactions.⁸⁶

Whereas; some degree of adverse effects may be unavoidable, their severity or incidence can be

significantly reduced through both physician and clinical pharmacist intervention and through educating patients.⁸⁷ The elderly population can obtain the benefits of pharmacologic therapy even when a drug regimen is a complex one, if drug regimens are tailored to meet the specific needs of each individual patient.⁸⁸

Physician and Clinical Pharmacist's Guide to Reducing Polypharmacy⁸⁹⁻⁹¹

1. Determine all medication being taken.
2. Identify the indication for all medications.
3. Identify any potential for adverse effect for each medication.
4. Recommend eliminating all medications with no therapeutic benefit, goal, when possible.
5. Recommend substituting medications with a lesser side – effect, profile when possible.
6. When possible, select agents with on in frequent dosing schedule.
7. Avoid utilizing another medication to treat a side effect of another agent.
8. Keep drug regimens as simple as possible.
9. Recommend starting at the lowest dosage and increasing slowly if necessary.
10. Review all medication profiles routinely.
11. Encourage patients to follow up with a physician regularly, particularly if they are experiencing side effects.
12. Encourage patients to carry the list of their medications to every physician appointment and update this list whenever changes are made to their medication regimen.

CONCLUSION

Polypharmacy is a widespread problem, and physician, clinical pharmacists, and patients are all responsible. Patients may contribute to the problem by self-medicating, failing to follow prescribed directions, failing to report all medications or OTC products used, and borrowing or trading medication with other persons. It is important to remember that the consequences of inappropriate Polypharmacy can be particularly significant to an elderly patient's well-being, financial security and ability to adhere to prescribed therapy.

A statement of Polypharmacy is needed at this time in order to:

- Promote periodic evaluation of drugs for efficacy
- Reduce adverse drug reactions
- Heighten awareness of health professionals regarding principles of geriatric prescription.

Prevention of unnecessary drug therapy problem can be conducted through reduction of drug use (it is



recommended to eliminate all medications without therapeutic benefit, goal or indication). Prevention of unnecessary drug therapy will also contribute in cost saving among elderly patients.

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