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Dangers of Polypharmacy

Pamela L. Valenza, Thomas C. McGinley,
James Feldman, Pritiben Patel, Kristine Cornejo,
Najmus Liang, Roopa Anmolsingh and
Noble McNaughton

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Abstract

Although the definition of polypharmacy has evolved over time, it has been and remains to be an issue in healthcare. With the prevalence of polypharmacy increasing, those in the health care field must remain vigilant of the adverse effects of medications and work to coordinate care and maintain appropriate prescribing practices. Here we present a clinical vignette that describes an encounter of a patient on multiple medications and the individual, provider, and systems-level issues that may have contributed to an adverse event resulting in a hospital stay. We will discuss the definition of polypharmacy, review the prevalence and economic implications of drug prescription practices, and examine the consequences and complications of polypharmacy in a number of different patient populations. We will discuss a number of scenarios involving polypharmacy that lead to medication errors, decreased quality of life, and patient harm, and then review evidence-based methods of interventions aimed at reducing the prevalence of polypharmacy and its associated complications.

Keywords: polypharmacy, risk factors, root causes, complications, interventions

1. Introduction

Although the definition of polypharmacy has evolved over time, it has been and remains to be an issue in healthcare. With the prevalence of polypharmacy increasing, those in the health care field must remain vigilant of the adverse effects of medications and work to coordinate care and maintain appropriate prescribing practices. Here we present a clinical vignette that describes an encounter of a patient on multiple medications and the individual,

provider, and systems-level issues that may have contributed to an adverse event resulting in a hospital stay. We will discuss the definition of polypharmacy, review the prevalence and economic implications of drug prescription practices, and examine the consequences and complications of polypharmacy in a number of different patient populations. We will discuss a number of scenarios involving polypharmacy that lead to medication errors, decreased quality of life, and patient harm, and then review evidence-based methods of interventions aimed at reducing the prevalence of polypharmacy and its associated complications.

2. Patient vignette

An 89-year old male presents to his primary care provider for follow-up after a recent hospitalization for a non-displaced hip fracture after a fall at home. He has poorly controlled hypertension, gastroesophageal reflux disease, hyperlipidemia, depression, prediabetes, arthritis, cataracts, and a remote history of heart disease with stents placed years ago. He reports two new medications were started in the hospital but he does not know why they were prescribed. The hospital did not fax over any records and the patient did not bring his discharge information summary to his appointment. At this time, he does not report any side effects of the new medicines but he would like to discuss getting treatment for ongoing fatigue, insomnia, and worsening joint pain. He reports seeing his cardiologist a couple months ago, who changed the dose of one of his blood pressure medicines but the patient is not sure which medicine was changed or the milligrams of the new dose. When asked to fill out a release of information to send to the cardiologist, the patient replies his cardiologist retired not long after his last appointment and the patient needs a referral to see a new cardiologist. In addition to a cardiologist, the patient also follows with a gastroenterologist, psychologist, psychiatrist, and ophthalmologist. None of the providers utilize the same electronic medical record system. On review of the list of medications the primary care provider has on file, the patient only recognizes eight out of sixteen medicines. In addition, his primary care provider personally prescribes only six of the medications on the list. When asked about compliance, the patient is adamant he always takes his medications as prescribed, but states his wife, who is currently at home, helps him take his medicines because he has some difficulty reading the labels and remembering to take them at the appropriate times.

3. Defining polypharmacy

Polypharmacy first appeared in the medical literature more than a century and a half ago [1]. Polypharmacy has multiple meanings without a clear consensus in the scientific community of a strict definition. This is most apparent in the wide range of research into the subject and how such data can be applied differently to various definitions of the term [2]. Defining polypharmacy can be further complicated by patients taking over-the-counter

medications and vitamins that are often not reported and as clinicians, it is not improbable to be treating patients with multiple conditions requiring multiple medications for optimal control. However, most clinicians would agree that polypharmacy is defined as the concomitant use of five to nine medications and hyperpolypharmacy, or excessive polypharmacy, is defined as the use of ten or more medications [3–5].

4. Drug prescription practices

Across all persons aged 20 or older, the prevalence of polypharmacy increased from an estimated 8.2% in 1999–2000 to 15% in 2011–2012 [6]. If the use of non-prescription medications is included, the prevalence of polypharmacy in the adult population increases to 29% [7]. The National Center for Health Statistics estimated that in 2014, approximately 2.8 billion prescription medications were ordered in the ambulatory office setting, of which the most frequently prescribed medications were analgesics, antihypertensives, and antidepressants [8]. Meanwhile, in the hospital outpatient departments, 329.2 million medications were prescribed with the most commonly ordered agents being analgesics, antidiabetics and antihyperlipidemics [8]. Overall, prescription drug use increased in many of the most common drug classes used by Americans including antihypertensives, antihyperlipidemics, antidepressants, antidiabetic agents, prescription analgesics, prescription proton-pump inhibitors, anticonvulsants, bronchodilators, and muscle relaxants [6]. Outpatient pediatric (aged ≤ 18) polypharmacy is also substantial with a prevalence rate of 10%, occurring more often in the setting of a complex chronic condition [9].

Individuals greater than 65 years old are the biggest consumers of medications; however, evidence shows that greater than 50% of elderly patients are taking at least one medication that is not medically necessary [10]. Nearly 40% of elderly adults take more than five prescription medications and almost 20% take more than 10 [6, 11]. Additionally, approximately half of the elderly population takes at least one over-the-counter drug and approximately half of the elderly population takes at least one nutritional supplement in combination with prescription medications [6, 11]. Polypharmacy declines in patients older than 85 years of age secondary to poor drug tolerance with age and increasing deprescribing practices as medical providers fear serious adverse drug reactions that may be more common in the very elderly [12].

5. Economic implications

In 2014, the United States (US) was estimated to have spent \$3 trillion on total national health care expenditures, of which 9.8% (\$294 billion) was spent on prescription drugs [8]. Approximately, \$77.7 billion was spent on total expenditures on Medicare Part D program in 2014, and an estimated \$165.1 billion will be utilized by 2022 [13]. This number will continue to increase as the estimated number of Americans >65 years of age by 2050 is projected to be 88.5 million, more than double that of 2010 (40.2 million) [14]. The US Center for Medicare and

Medicaid Services (CMS) states that polypharmacy has been estimated to cost US health plans over \$50 billion annually [8, 15, 16]. With respect to medication discrepancies and patient adherence, if patients took all appropriate medications exactly as prescribed, it is estimated it would save 13% (\$290 billion) of total US health care expenditures due to avoidable medical costs [17].

An estimated \$16.4 billion and \$4.2 billion are spent on inpatient and outpatient preventable medication errors, respectively [18]. Adverse drug events (ADEs) occur commonly in hospital settings, which in turn increase the likelihood of morbidity, length of stay (LOS), and the cost of care. A multicenter retrospective cohort study conducted in six community hospitals significantly showed that ADEs are associated with an increased adjusted average hospitalization cost of \$6910 and increased length of stay of 5 days [19]. The severity of ADEs are associated with further increased costs and length of stay (\$9768 in patients and LOS 7.79 days with significant ADEs versus \$15,033 in patients and LOS 10.56 days with life-threatening ADEs) [19]. Research evaluating the effect of computerized provider order entry (CPOE) in the outpatient setting has shown the potential to result in fewer medication errors and ADEs by 1.5 million and 14,500, respectively, with the potential to save \$18 million dollars [20]. In the hospital setting, the implementation of CPOE is associated with an estimated 50% reduction of ADEs and medication errors [21].

6. Root causes of polypharmacy

The prevalence of polypharmacy is multifactorial with risk factors spanning from the individual/patient level (increasing longevity, coexistence of chronic medical conditions, availability of over-the-counter drugs, use of more than one pharmacy) to the physician level (medical guidelines, prescribing practices) to systems-level issues (multiple prescribing providers, electronic medical records, transitions of care) [22]. See **Figure 1** for a comprehensive list of the factors associated with polypharmacy [23, 24]. Medical practitioners rely on clinical guidelines to guide their medical practice and clinical decisions to provide the best care to patients. Available clinical guidelines are usually devised with focus on a single disease and often overlook the possibility of comorbidities and the consumption of other medications by the patient [1]. Adherence to clinical guidelines for multiple concomitant chronic conditions may inadvertently lead to adverse outcomes for patients due to complications from multiple medications for multiple medical conditions [25]. In the post-acute transition of care setting, patients can often see their medication list expand or see changes in dosages due to their recent debilitation and hospitalization [3]. There are often multiple clinicians, sometimes in the form of multidisciplinary teams, making medical decisions. Lack of communication between treatment teams and disruption in communication during transitions of care from the inpatient setting to the outpatient setting and vice-versa can precipitate polypharmacy [23]. If we look at our patient in the clinical vignette, there exists several risk factors for polypharmacy: elderly age, multiple chronic conditions, decreased ability to function, multiple providers, poor physician-patient communication, poor physician-physician communication, multiple prescribers, and disjointed electronic medical records.

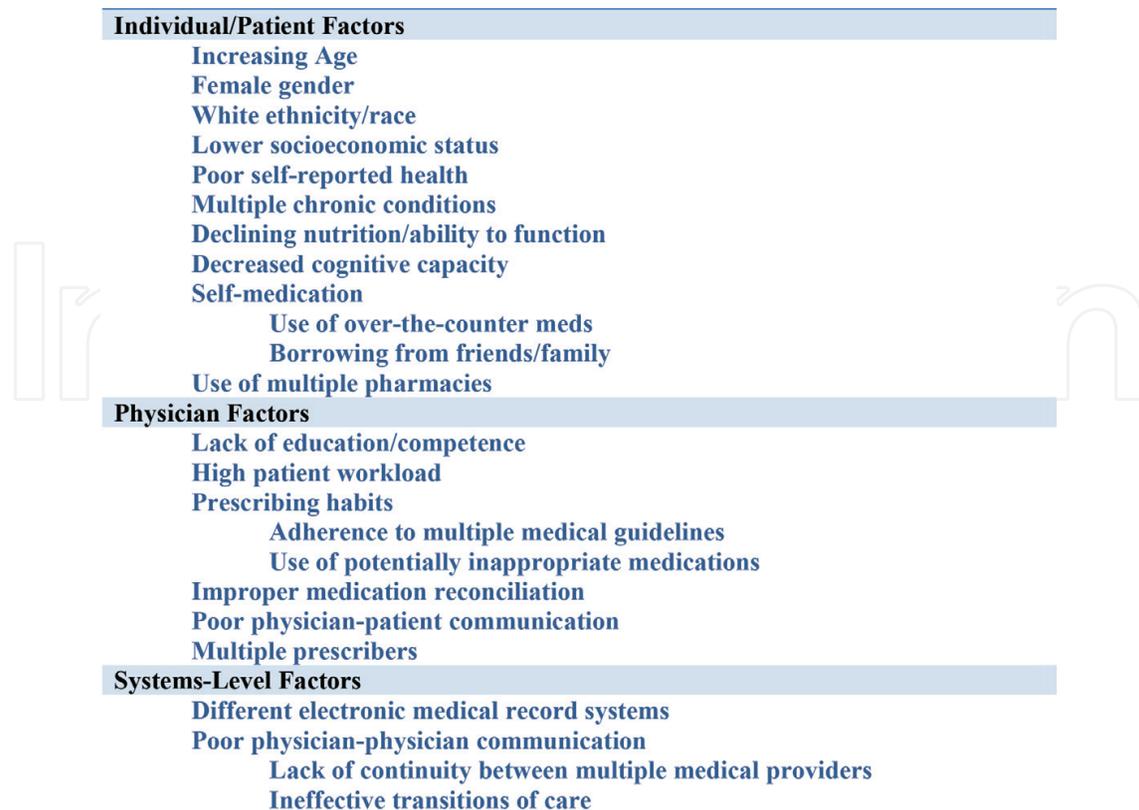


Figure 1. Factors associated with polypharmacy.

7. Polypharmacy complications and consequences

The more drugs an individual takes, the more likely he or she will suffer a complication or adverse outcome [4]. Polypharmacy is associated with increases in many adverse outcomes including adverse drug reactions, drug to drug interactions, drug to disease interactions, non-adherence, falls, cognitive impairment, hospital admission and mortality [4, 12, 26].

Adverse drug reactions (ADRs) are defined as undesired or noxious effects of standard drug treatment doses which include amplified drug effects, side effects, interactions with other drugs and interactions with other nutrients or diseases [11]. ADRs are a common cause of hospital admissions and emergency department visits [27, 28]. Many factors contribute to adverse drug reactions including unnecessary drug use, inappropriate drug choice, therapeutic duplication, inappropriate dosing regimen, physician-patient communication, and long-term medication use without periodic review [26, 29].

In the hospital setting, polypharmacy is a strong predictor of adverse drug reactions in both adults and pediatrics [30]. Not only are hospitalized adults at risk of adverse events from potentially inappropriate medications or drug-drug interactions, patients with polypharmacy are at higher risk due to medication discrepancies that may result from unintended discrepancies in actual regimen versus recorded regimen during transitions from outpatient to inpatient and vice-versa, changes to medication regimens while in the hospital, and poor

communication of medication changes to both patient and next provider of care [31]. Large numbers of hospitalized pediatric patients are exposed to polypharmacy with increased risk associated with longer lengths of stay and presence of complex chronic conditions [32, 33]. Polypharmacy increases potential drug–drug interactions in pediatrics, often due to off-label prescribing of drugs, lack of therapeutic profiles for less common medications, and weight-based medication errors [34].

Medical record discrepancies in the outpatient setting occur in about 75% of cases, with a strong positive correlation with polypharmacy, with rates escalating as high as 95% [17]. Discrepancies may include active prescriptions that the patient did not include on their medication record or patient-reported medications that were not documented in the electronic health record. Adverse events due to medical record discrepancy occur not only from failure to perform reconciliation, but failure to ensure and promote patient adherence to the regimen as intended by the provider [17].

Medication errors cause at least one death every day and injure 1.3 million people annually in the United States [35]. Several factors contribute to medication errors secondary to polypharmacy. Errors can easily occur when patients are seeing multiple specialty providers for comorbid conditions. Nearly 40% of all medication errors and 50% of adverse drug events are a result from errors in prescribing such as overdosing of medications, underdosing of medications, allergies, improper dose, improper drug, and duplication of therapy [36]. Lack of communication and coordination between treating providers increases the likelihood of prescribing medications which may result in adverse drug reactions, side effects or worse. Failing to review patient records and reconcile medications at regular visits by all providers poses greater risk for the occurrence of errors [37]. Omission of performing adequate medication reconciliation, including asking about over-the-counter medications, herbals, vitamins, and nutritional supplements, and patients' failure to disclose other medication use may contribute to the occurrence of a preventable harmful drug-drug interaction [38]. To ensure accurate medication reconciliation, patients should be asked to bring all medications to each provider visit [39].

Transitions of care pose a danger of medication errors and include a change in setting, practitioner, type of service and move from one level of care to another [40]. Ineffective processes during transitions of care can result in adverse events and higher hospital readmission rates and costs [41]. During transitions of care, patient education regarding complicated regimens, lack of accountability of the clinical entity to provide coordination across settings, and lack of effective communication between providers are most often the root causes [42, 43].

Patient adherence to polypharmacy regimens presents another juncture at which errors may arise. Adherence is defined as the extent to which an individual's behavior, including taking medicine, following a certain type of diet, or lifestyle modifications, corresponds with recommendations from a healthcare provider as agreed upon by the patient [44]. Nonadherence is defined as the improper intake of medication [44]. The complexity of a medicine regimen is inversely related to medication adherence with increasingly complex regimens (increased frequency of dose, decreased patient education) associated with lower rates of adherence [45]. Issues of adherence include patients who do not fill their prescriptions, decide to stop taking

medications, or fail to take one or more medications as prescribed [40]. These issues occur for a variety of reasons including financial hardship, symptom improvement, and unreported side effects.

Accidental inappropriate drug use may result from erroneous or repeat doses from poor eyesight or forgetfulness [46]. In addition, patients may not be able to accurately read and understand the labels on medications prescribed. With more than 33,000 trademarked medications, errors have commonly been linked to drugs with similar sounding names. Adding to the drug name confusion, are problems with similar packaging and labeling, incomplete knowledge, illegible handwriting, prescriptions which are orally communicated and a significant number of new products continually being introduced into the marketplace [47].

8. Special considerations in different patient populations

The following sections briefly touch on unique considerations when addressing polypharmacy in different patient populations and certain medical conditions.

8.1. Elderly/end of life

Older adults with comorbidities are often excluded from drug trials, therefore, the use of drugs in older populations to a large extent can be considered experimental [48]. The use of multiple clinical guidelines that do not account for multiple comorbid conditions, along with the knowledge of altered pharmacodynamics due to the physiological changes in older adults, can become dangerous to the elderly patient. Certain classes of drugs have been associated with cognitive impairment and falls, with elderly patients being more susceptible than others. Polypharmacy in elderly patients has been shown to be a predictor of frequent hospitalizations, nursing home placement, death, hypoglycemia, fracture, impaired mobility, pneumonia, and malnutrition [22]. As the elderly age, they are at increased risk of complications from polypharmacy including the inability to effectively metabolize and excrete multiple medications due to changes in liver and kidney function [22]. To confound this further, age-related change in pharmacodynamics resulting from changes in drug receptor affinity alters the concentrations of drugs that are effective and toxic [49]. Additionally, increasing use and number of medications seems to have a negative impact on nutrient intake and nutritional status overall in the elderly not only from drug-nutrient interactions, but also from compounded side effects such as nausea, decreased appetite, dry mouth and metallic taste which ultimately decrease food intake [46].

In elderly patients at the end of life, pain is a common symptom [50]. Patients undergoing palliative treatment are especially vulnerable to unwanted adverse effects of medications secondary to their altered metabolism, organ dysfunction, and high likelihood of polypharmacy with ensuing drug-drug and drug-host interactions [51]. In one study, potential drug-drug interactions (DDIs) were detected in 61% of inpatient hospice patients [52]. Polypharmacy was the major predictor for DDIs and the most commonly implicated drugs in therapeutically potential DDIs were antipsychotics, antiemetics, antidepressants, insulin, glucocorticoids,

cardiovascular drugs and NSAIDs [52]. In elderly patients, the remaining life expectancy of the patient should be considered when prescribing medication, as benefits of certain medications may not be valid or may not outweigh risks in a patient with a lower life expectancy. As patients age, it may be important to consider de-prescribing to optimize the patient's total health and reduce unnecessary polypharmacy [48].

8.2. HIV population

With the evolution and advancement of antiretroviral therapies worldwide, HIV is now being considered a chronic disease. Life expectancy for HIV patients has been shown in recent years to closely approximate that of non-infected HIV persons [53]. The HIV population is also aging. Statistics show over 10% of HIV positive persons globally are over the age of 50, with projected data estimating this to increase by an additional 20% in the next 15 years [54]. In the United States alone, it is estimated that more than half of persons living with HIV are ≥ 50 years old [55]. In 2010, the prevalence of polypharmacy in persons living with HIV was estimated to be 35%, surpassing that of persons not living with HIV [55]. HIV patients have been noted to have greater cardiovascular, renal, neurologic, oncologic and osteoporotic disease despite having decreased viral loads or increased CD4 counts [56]. Presence of age-associated comorbidities increases the risk of polypharmacy in HIV patients, with higher rates of prescriptions for gastrointestinal, neurologic, respiratory, analgesic, or anti-infective drugs than the general population [57]. Antiretroviral therapy has a high risk for DDIs and toxicity, and optimizing management to address this risks and decrease pill burden can be difficult [54]. In older HIV patients, 77% are at risk of potential DDIs due to polypharmacy, with the highest risk in patients with concomitant cardiovascular drug use [58].

8.3. Kidney disease and liver disease

There is a high incidence of polypharmacy in patients with chronic kidney disease (CKD) [59]. Significant medication-related problems, including drug-drug interactions, high incidence of adverse drug reactions (ADRs) and low adherence have been noted [60]. Complex medication regimens may be necessary in CKD to treat related comorbid conditions, however patients are at high risk of DDIs, especially due to changes in pharmacokinetic and pharmacodynamic parameters associated with decreased kidney function, and therefore require constant adjustment of medication doses accordingly [61]. Complicated medication regimens and concerns about side effects were frequently cited as a cause of low or non-adherence in patients with CKD [62]. Additionally, use of certain contraindicated over-the-counter or herbal remedies may put the patient at increased risk of adverse drug events and interactions due to interference with CKD medications [63].

Liver pathology is of special importance especially when treatment of disease includes polypharmacy. Multiple drug regimens have shown to cause development of various forms of hepatotoxic reactions, and many patients with cirrhosis often have complicated medication regimens and are at higher risk for complications from polypharmacy [64]. Frequent reassessment of the patient's baseline renal and hepatic function, medication properties, doses administered and length of therapy are helpful in achieving reduction in DDIs and ADRs [65].

8.4. Mental illness

Prescribing patterns in the adult outpatient psychiatric setting show the median number of prescriptions prescribed per visit have doubled, largely with increased psychotropic polypharmacy (defined as ≥ 2 psychiatric medications in the same patient) with antidepressant and antipsychotic prescriptions in adults aged 45–64 [66]. Additionally, this number may be an underrepresentation in patients who see multiple providers [66]. Psychotropic polypharmacy is also increasingly seen in the outpatient pediatric population with prevalence estimates ranging from 13 to 35% [67–69]. In this population of patients, both psychotropic and non-psychotropic drugs contribute to polypharmacy and brings with it, the associated complications. Low adherence, noncompliance, ADRs, and DDIs contribute to the detrimental effects of multiple drug therapy. In this cohort, polypharmacy increases the risk of potentially inappropriate medication (PIMs) administration, and prolonged polypharmacy can have significant cognitive-impairing effects [70].

8.5. Intellectual and developmental disabilities

Patients with intellectual disabilities are reported to have more than twice as many health problems as the general population and a higher rate of comorbid somatic or mental health disorders [71]. There is a considerably wide range of prevalence of polypharmacy noted in the literature for this population [72, 73]. Similarly to other patient populations, the larger the number of comorbidities, the more likely there is to be polypharmacy and all its associated complications. Specific to this patient population, living in a residential facility and increasing severity of intellectual disability increases risk of exposure to polypharmacy [71]. Affective disorders, psychoses, and anxiety are the three leading co-morbid mental health disorders among adults with intellectual disabilities [74]. However, it may be difficult to make a distinction between the disorders based on behavioral patterns or traditional diagnoses which may contribute to overuse or underuse of medications [74].

8.6. Chronic pain

Chronic pain has been estimated to affect 116 million adults and costs \$560–\$635 billion annually in the US [75]. There is a multimodal approach utilized for chronic pain that includes nonpharmacological and pharmacological interventions. Previous studies have reported that patients diagnosed with chronic lower back pain or osteoarthritis, and who were prescribed an analgesic such as an opioid, have overall higher health care costs [76, 77]. When looking at more recent literature, the increased financial impact of chronic non-cancer patients continues to persist [78]. Costs for chronic non-cancer pain patients are increased both in older and younger patients, likely secondary to complications from increased drug-drug exposure (DDE) and increased prescription costs related to polypharmacy, respectively [79]. In patients on chronic opioids, the risk of DDE increases with each additional medication a patient is prescribed, with a rate greater than 60% in patients taking four or more prescription medications compared to 14% in patients taking no other prescription medications [80]. Therefore, addressing polypharmacy in chronic pain patients may be an important component in reducing both total medical costs and the risk of drug-drug interactions.

9. Interventions to reduce polypharmacy

There is a growing body of research regarding the development of evidence-based interventions to reduce polypharmacy, inappropriate prescribing, and patient nonadherence. While many of the published tools and interventions have focused on the elderly population, the evidence-based studies encompass numerous themes involving various strategies. The themes include interventions to:

- Address appropriate versus inappropriate prescribing
- Strengthen patient education and patient-physician communication
- Promote better medication reconciliation
- Ameliorate high-risk error areas such as transitions of care
- Enhance physician to physician communication and interprofessional collaboration
- Reduce nonintentional nonadherence by patients.

9.1. Appropriate versus inappropriate prescribing patterns by physicians

A concept that has been discussed in the literature when addressing reducing complications of polypharmacy deals not just with the number of medications, but also with the appropriateness of the treatment regimen. Several guidelines have been established evaluating clinical necessity of medications, irrespective of the number of medications. The theory behind addressing the appropriateness of prescribing and not just the absolute number of medications is that patients with multiple comorbidities may, in fact, necessitate a number of medications, thus being clinically appropriate polypharmacy. Additionally, patients may experience adverse drug events on fewer medications, however they may not get identified through current screening protocols based strictly on number of prescriptions [81].

There are a number of evidence-based studies advocating the use of computerized alerts to decrease potentially inappropriate medications. Using an automated clinical decision support system in an electronic medical record system to prompt physicians to update patient problem lists during inpatient computerized physician order entry can result in increased updated problem list accuracy at a rate of about 95% [82]. That being said, recent studies report between 69 and 91% of medication alerts were overridden by physicians as the alerts were considered irrelevant by the prescribing physicians [52]. Electronic medical record-based interventions have also achieved a significant reduction in the number of medications initiated during the intervention period [83]. Medical decision-making tools and checklists have also been utilized to reduce potentially inappropriate prescribing. Checklists used by physicians to support therapeutic reasoning of the physicians in order to improve the quality of drug prescriptions have resulted in a 22% reduction in the risk of ≥ 1 of potentially inappropriate medication being prescribed at discharge [84].

There are also a number of published studies advocating the use of review of patient medications to decrease polypharmacy and potentially inappropriate prescribing [85, 86]. Increased

patient-physician medication reviews have utilized physician notifications about high-risk patients, “medication management” reports listing information regarding patient prescriptions, and clinical practice guidelines for preventing and managing inappropriate prescribing resulting in about half of all physicians making at least one change in the patients’ medication regimens [87]. These guidelines encouraged “brown bag” medication reviews of medications, including non-prescription medications, during patient office visits. As a result, 20% of patients recorded discontinuation of medication, 29% reported a change in medication and 17% reported taking medication that their physician was unaware of [87]. While numerous studies have demonstrated successful interventions in deprescribing potentially inappropriate medications, there is a paucity of data causally linking generalized deprescribing to clinically significant improvements in hospital admissions, mortality, and patients’ overall quality of life [88, 89]. However, targeted patient-specific interventions may have a role in reducing mortality [89]. In elderly patients undergoing a deprescribing protocol, there was a successful reduction in the number of regular medicines taken by elderly patients in residential care settings with no significant adverse effects on survival or other clinical outcomes [90].

Collaborative interdisciplinary teams have been used to improve the quality of care given to patients. The concept of Comprehensive Geriatric Assessment (CGA) is a multipronged approach to provide integrated care of elderly patients through the use of interdisciplinary teams. These teams assess medical, psychosocial and functional capabilities of elderly patients and often include physicians, social workers, nurses and other healthcare providers [91]. CGA uses protocols to assess functional, cognitive, affective, and nutritional status as well as caregiver and social support. CGA also assesses for geriatric problems such as incontinence and falls, and pays particular attention to medication management with a goal of decreasing adverse drug events [91, 92]. Utilizing multidisciplinary teams have been shown to reduce serious adverse drug events by 35% when compared to those in usual care [86].

Many researchers have also looked at the use of validated tools (e.g., Beers criteria, Medication Appropriateness Index [MAI], Screening Tool of Older Persons Prescriptions [STOPP], Screening Tool to Alert Doctors to Right Treatment [START]) to identify elderly patients at risk for high-risk prescribing practices. In older patients with a potentially preventable medication-related hospital admission, the use of STOPP/START 2008 criteria resulted in a 34.1% decrease in potentially inappropriate medications and a 57.7% decrease in potential prescribing omissions [93]. The Beers criteria, based on a consensus panel of experts, has been used for many years in United States as a guide to assist health care practitioners in determining whether or not certain medications may be unsafe for use in the elderly [26]. Altering or adjusting clinical targets may also have a benefit in discerning appropriate versus inappropriate medication prescribing. It appears that setting strict clinical targets in some populations may have adverse outcomes. In the famous Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, there was an increased risk of hypoglycemia, adverse events and death in those with tight glycemic control [94]. By liberalizing our clinical targets, we may decrease medication use and improve clinical outcomes with regards to certain medications and certain groups of patients.

9.2. Strengthen patient education and patient-physician communication

In the vignette above, the patient was not educated appropriately regarding the new medications he was prescribed nor did he appear to have a good understanding of his overall medication regimen. While health care professionals are most frequently viewed as integral to smooth transitions of care, patients and caregivers, and their understanding of treatment needs and readiness to actively participate, are essential to the process. Patient education and understanding of their conditions, necessary treatments, and the importance of follow through with recommendations are key in helping to promote a more seamless flow of movement during transitions of care. Implementing patient education is a potential intervention for reducing the rates of polypharmacy [88]. Educational packets or patient information leaflets, specifically designed and targeted according to patient literacy can improve outcomes and effectively manage polypharmacy [95]. Educational materials can be in various forms including but certainly not limited to videos, individual or group teaching sessions and teach back techniques [96].

The EMPOWER [Eliminating Medications Through Patient Ownership of End Results] study that evaluated a benzodiazepine therapy cessation program found that after 6 months, patients aged 65-95 had a 27% discontinuance of their use of benzodiazepines in comparison to 5% in the control group [97, 98]. Through the EMPOWER study, it was demonstrated that consumer education is directly related to effectively eliciting shared decision-making around the overuse of medication. The patient-centered process aims to reinforce known enablers and address barriers to medication cessation. This increases the shared responsibility in decision-making with healthcare providers [99]. Therefore, direct patient education can effectively stimulate shared decision-making around overuse of medications that increase the risk of harmful effects.

9.3. Promote better medication reconciliation

Medication errors and other adverse events during care transitions led the Joint Commission to identify medication reconciliation as a National Patient Safety Goal in 2005 [37]. In 2014, the requirement to inform patients regarding the importance of maintaining updated medication information was added to existing safety goals [100]. The use of interventions to improve medication reconciliation has had direct and positive effects on clinical outcomes. Improvement in electronic medication reconciliation has also been shown to reduce the incidence of medication discrepancies during transitions of care in hospitals, especially regarding medication omissions but also including other areas such as medication error dosing [101]. Some of these interventions have used pharmacists while others have relied on the electronic medical record interventions or other healthcare providers. Hazra and colleagues showed a threefold decrease in the prevalence of antipsychotic polypharmacy after a pharmacist-led intervention provided education to prescribers [102]. Milos and colleagues performed a randomized controlled clinical trial in nursing home patients ≥ 75 years of age where medication reviews by clinical pharmacists based on nurse-initiated symptom assessments provided feedback to physicians [103]. Two months after the medication reviews, the number of patients in the intervention group with at least one potentially inappropriate medication and

the number of patients using 10 or more medications had decreased [103]. Mekonnen and colleagues performed a meta-analysis of pharmacist-led medication reconciliation programs on clinical outcomes at hospital transitions involving 19 studies, including 11 randomized controlled trials [104]. A total of more than 15,000 patients were included in the data. The results revealed that pharmacist-led interventions were effective strategies to reduce medication discrepancies with a greater impact on admission and discharge transitions as compared to other hospital transitions of care [104]. Additionally, patients should also be encouraged to carry a list of their medications with them for emergencies and visits to all providers [100].

9.4. Ameliorate high-risk error areas such as transitions of care

“The root cause of adverse events associated with transitions of care is poor transfer of information between providers” [105]. Multiple studies demonstrate that improving communication to enhance coordinated care during transitions can result in more cost-efficient care, reduced rate of errors and near misses, and improved patient satisfaction [106–108]. Communication of essential patient medical information among treating providers within and between health care settings is paramount to ensuring safe and comprehensive transitions of care. Several components have been identified which are felt to be key in reducing adverse events as patients move from one level or setting of care to another. As electronic health records have become the primary tool for documenting and storing patient information, they can facilitate the timely sharing of information required for continuity of care [109]. The primary mode of communication with the highest rates of direct transfer of patient information from one provider to another occurs via telephonic communication, with successful communication occurring approximately 70% of the time [110]. Additional interventions, which have been implemented to improve patient care during transitions of care, include patient education, the scheduling of outpatient visits prior to discharge and telephone follow-up. Further, scheduling follow-up appointments with a primary care physician in a timely manner and, when available, home visits, all serve to help provide a greater structure for a more seamless transition [100].

The role of pharmacists has become a greater focus of attention as part of the care team and as a component of the discharge or transition of care for patients. Evidence exists which supports the benefits of involving pharmacists in the process of medication reconciliation at various point of transitions including admission, transfer from the ICU, and upon and following hospital discharge [111–113]. Pharmacists play a significant role in education for both patients and their caregivers. They are uniquely qualified to clearly explain why specific medications have been recommended, and why these medications are the most appropriate for each patient. While it is clear other health professionals can provide such information, pharmacists more likely possess the greatest insight as to the reason for specific medications targeted to a patient’s condition [114].

There are currently several emerging models of care designed to address various interventions and resources to help ensure safe transitions for patients and caregivers. The focus of these efforts is to enhance patient safety, improve communication and reduce hospital readmissions. Two notable models include The Care Transitions Intervention and The Transitional Care Model [115, 116].

9.5. Enhance physician to physician communication and interprofessional collaboration

In order to overcome obstacles to reduce polypharmacy, it is imperative to communicate with patients and healthcare providers to understand what their perceptions of those obstacles are and how to work together to overcome them. Palaygi and colleagues performed a qualitative study in long-term care facilities involving focus groups to address perceptions of medication use and deprescribing [117]. Deprescribing was defined as withdrawal of inappropriate medications with the goal of reducing polypharmacy. The focus groups included physicians, pharmacists, nurses, patients, and relatives. All participants acknowledged the burden of too many medications, yet displayed passive tendencies toward reduction. The primary care physician was the central trusted figure in medication initiation and alteration. The primary care physicians complained of systems barriers including poor medical record uniformity, time constraints, challenges with staff and pharmacy collaboration, and the effects of multiple prescribing specialists as obstacles to deprescribing [117]. Skinner conducted an extensive literature review looking for polypharmacy protocol for primary care. Mnemonics, algorithms, clinical practice guidelines, and clinical strategies for addressing polypharmacy were noted, as well as the use of screening instruments for assessing potentially inappropriate medication prescribing [118]. However, there appears to be no standard protocol to address polypharmacy [118]. From these two publications, many problems were identified. However, the importance of communication, particularly physician to physician communication, as well as the need for a standardized polypharmacy protocol, particularly involving deprescribing, seemed to represent the most challenging obstacles in overcoming barriers to successful polypharmacy reduction. Farrell and colleagues have set out to develop guidelines for deprescribing [119].

Additional studies also point out the need for better interprofessional collaboration and communication among other problems. The main concerns and perceptions by general practitioners of factors involved in contributing to polypharmacy include difficulty in keeping exact medication intake lists, challenges in overcoming patients' strong beliefs in their medications and in self-medicating, the involvement of multiple prescribers, the lack of regular medication reviews and revisions, and the pressures placed upon physicians in using medications based upon evidence-based protocols [120]. Lavan and colleagues published a review article about reducing prescribing errors in elderly patients and noted that published data support a few interventions including prescriber education in pharmacotherapy, application of STOPP/START criteria to reduce potentially inappropriate prescribing, electronic prescribing, and a close liaison between pharmacists and physicians to perform structured medication reviews and reconciliations [121].

9.6. Reduce nonintentional nonadherence by patients

75% of Americans have difficulty taking their medication as prescribed with the cost of nonadherence ranging from \$100 billion to \$300 billion every year [122]. Intentional nonadherence refers to the patient making a certain amount of decision-making in their care often based on their trust in their medical provider and knowing the effects of their medications [44]. The patient's adherence improves when patients feel well informed about their illness and the importance of necessary treatment [44]. In patients over 65 years of age, the most significant predictors for non-intentional non-adherence are forgetfulness and carelessness [123].

Others factors that may impact adherence include medication beliefs, increasing numbers of chronic diseases leading to complicated regimens, and sociodemographic factors such as high costs, co-payments, and lack of understanding [122, 124]. The utilization of cue-based interventions (i.e., phone reminders or alarms) may be helpful for forgetfulness but less likely to reduce non-adherence due to passive inconsistent behaviors [123, 125]. Health literacy interventions can improve patients' education regarding their medications and therefore potentially improve the patients' role in their management of medications. The importance of assessing patient literacy and readiness to be an active member of the health care team is the responsibility of the health care system. A health literacy pilot study found that 40% of patients had a low health literacy, which is defined as below 9th grade reading level [126]. After just 3 months of one patient literacy intervention, patients' self-reported adherence had improved [126].

10. Conclusion

Polypharmacy is a multifactorial, complex issue. There are a number of targeted interventions that focus on addressing a variety of determinants with varying levels of evidentiary support. Optimizing prescribing, reducing potentially inappropriate medications, and minimizing risk is a common theme across all interventions, however implementation must be highly individualized for each patient.

Author details

Pamela L. Valenza*, Thomas C. McGinley, James Feldman, Pritiben Patel, Kristine Cornejo, Najmus Liang, Roopa Anmolsingh and Noble McNaughton

*Address all correspondence to: pamela.valenza@sluhn.org

Department of Family Medicine-Warren, St. Luke's University Health Network, Phillipsburg, NJ, USA

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