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ORIGINAL ARTICLE

Conceptualizing multiple drug use in patients with comorbidity and multimorbidity: proposal for standard definitions beyond the term polypharmacy

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Abstract

With older and aging populations, patients experience multiple chronic diseases at the same time. Individual chronic disease guidelines often recommend pharmacological therapies as a key intervention, resulting in patients being prescribed multiple regular medications for their different diseases. Although the term ''polypharmacy'' has been applied to the use of multiple medications, there is no consistent definition, and this term is now being used all inclusively. To improve both scientific rigor and optimal patient care, it is crucial that a standard terminology is used, which reclassifies the term ''polypharmacy'' into distinct phenotypes relating to the index chronic disease, additional conditions to the index (comorbidity), or the experience of multiple chronic conditions at the same time (multimorbidity). Using three exemplar index conditions; heart failure, type 2 diabetes, and breast cancer, we propose the reclassification of the term ''polypharmacy'' into three distinct phenotypes. First, index drug or multi-index drug therapy, where each index condition creates multiple drug use for that condition; second, codrug therapy, where addition of other comorbid conditions increases the multiple drug use and may influence the management of the index disease and third, multidrug therapy, where adult population with multimorbidity may be on many drugs. This article reviews guidelines for the individual exemplars to develop the basis for the new terms and then develops the pharmacoepidemiology of multiple drug use further by reviewing the evidence on the relationship between the phenotypic classification and important outcomes. The importance of standardizing ''polypharmacy'' terminology for the scientific agenda and clinical practice is that it relates to an index condition or disease safety outcomes including drug interactions, adverse side effects in hospital admissions, and related ''polypill'' concept.

Keywords: Diabetes; Heart failure; Breast cancer; Polypharmacy; Comorbidity; Multimorbidity

1. Introduction

Drugs play a key role in the routine management of chronic diseases including preventing progression and improving prognosis, management of physiological symptoms (e.g., pain), and improving mental health problems [1]. Some of the many different examples include the endocrine system (e.g., diabetes) [2], cardiovascular system (e.g., heart failure) [3], and now increasingly cancer [4], which, with improving prognosis, is also managed as a chronic long-term condition. The current evidence-based approach to clinical management has meant that multiple drug prescribing has been translated into routine clinical practice via national and local guidelines [5–7].

Individual chronic disease guidelines often include recommendations on different medications, and the implementation of each guideline results in a patient with at least two or more drug classes, often initiated at the onset for treatment, control, or the prevention of linked diseases. Yet, the individual patient

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What is new?

Key findings

- The article proposes alternative terminology for polypharmacy, which links the use of multiple drugs to comorbidity and multimorbidity using three exemplars.

What this adds to what is known?

- The term polypharmacy is applied to a variety of clinical scenarios and in particular to the use of multiple drugs in the same person. However, it does not meet the scope or scientific rigor needed for clinical practice or research.

What is the implication and what should change now?

- The benefits of the proposed more sensitive definition relate to scientific rigor to compare evidence using a more structured and standard definition and measure efficacy of outcomes following drug intervention models and better understanding of case mix when classifying diseases and drug treatments in populations.
- The three distinct phenotypes proposed are (i) index drug or multi-index drug therapy, where each index condition creates multiple drug use for that condition; (ii) codrug therapy, where addition of other comorbid conditions increases the multiple drug use and may influence the management of the index disease; and (iii) multidrug therapy, where adult population with multimorbidity may be on many drugs.

experience is often of two or more chronic conditions at the same time, which is an issue not just for the old but for the larger population experiencing chronic diseases. Therefore, people experiencing multiple diseases will have an escalating number of drugs for each individual condition. This phenomenon has been increasingly cited in literature [8,9], and many studies have been incorporating the use of multiple drugs by patients under the umbrella term ''polypharmacy'' [10,11]. However, there are problems with this approach as the term ''polypharmacy'' has varied meanings, which include the number of drugs, any medications associated with aging, or the adverse events for multiple drug combinations [12]. For example, in a systematic review, over 80% of studies had used different numerical values to define polypharmacy, and the remainder had used alternative definitions relating to the care context or other descriptive statements [11]. The term ''polypharmacy'' in practice and research has come to be an inclusive generic term for any type of terminology, which reduces the ability to observe more complex relationships between specific drug combinations and outcomes [13] or to compare studies that have used different criteria and definitions. The other key scientific gap is the lack of any clear definitions, which link the specific combination of multiple chronic diseases to the prescribing or use of multiple drugs. This link is crucial as the status of the chronic disease and the use of drugs as an intervention are implicitly linked to evidence for future clinical and health care outcomes.

In scientific literature, people who experience multiple chronic diseases have been defined into the distinct but related concepts of comorbidity or multimorbidity. Comorbidity is defined as the study of a primary index disease in the context of the other diseases, or as the consequence, but multimorbidity is defined as the experience of two or more chronic diseases by an individual [14]. Despite clear epidemiological and increasingly clinical approaches to the experience of multiple conditions, no such definitions have been applied to multiple drug use in an individual or how multiple drugs might link to the disease status. There is a clear necessity that the experience of multiple chronic conditions and the associated scale of drug use in the larger population require standard definitions. The term ''polypharmacy'' fails to meet the scope of this topic, and this umbrella term needs to distinguish between disease indications for drug treatment and ''polypharmacy'' in older populations.

In the following sections, three empirical examples of type 2 diabetes, heart failure, and breast cancer are used to delineate the concepts by using the current evidence-based guidelines, and the implications of multiple drug use for each condition are drawn out. A case with all three conditions is then used to illustrate the links between disease, multiple diseases and multiple drug use, concluding with a proposal for standard definitions and epidemiological approaches to multiple drug use in adult populations (Table 1).

2. Chronic disease guidelines and drug recommendations

2.1. Type 2 diabetes mellitus

2.1.1. Clinical context

In patients with established type 2 diabetes mellitus, patients will often start with a biguanide (e.g., metformin) but alternative will include sulphonylurea (e.g., Gliclazide) [2,5]. If the patient remains poorly controlled, then there may either be the addition of insulin or other oral antidiabetic drugs. In terms of prevention approaches, other adjunct drugs that may be rapidly initiated are aimed at the reduction of cardiovascular outcomes, and renal or ocular complications. In patients with type 2 diabetes, at the age of 45 years, it is estimated that around 40% have hypertension and by the age of 75 years around 60% have hypertension or comorbid cardiovascular and renal complications [15,16]. So the

Table 1. Linking disease status to drug phenotypes

Disease definitions	Disease status	Drug phenotypes	Indicator drugs
Index disease	Diabetes mellitus type 2	Index drug therapy	Biguanide
		Index multidrug therapy	Biguanide, sulphonylurea, or insulin
Comorbidity	Hypertension, cardiovascular disease	Codrug therapy	Antihypertensives (specifically ACEi), lipid-lowering drugs, other chronic diseases
Multimorbidity	Diabetes mellitus, hypertension, chronic kidney disease, plus other chronic conditions	Multidrug therapy	Biguanide, sulphonylurea, insulin, antihypertensives, lipid-lowering drugs
Index disease	Heart failure with LVSD	Index drug therapy	ACEi and Beta-blocker
		Index multidrug therapy	ARB, Aldosterone Antagonists, Digoxin, Hydralazine/Nitrate Diuretics
Comorbidity	Atrial fibrillation, ischemic heart disease	Codrug therapy	Nitrates, anticoagulants, aspirin, statins, amlodipine, amioderone, digoxin
Multimorbidity	Heart failure, hypertension, chronic kidney disease	Multidrug therapy	ACEi, beta-blockers, diuretics, nitrates, digoxin, and other drugs
Index disease	Breast cancer	Index drug therapy	Chemotherapy
		Index disease multidrug therapies	Combination chemotherapy
Comorbidity	Organ involvement	Codrug therapies	Antiemetics, corticosteroids, iron
Multimorbidity	Breast cancer, cardiovascular, renal, or bone disease complications	Multidrug therapies	Cancer, symptom, chronic disease, antidepressants
Index chronic disease	Breast cancer in remission	Index follow-up therapy	Tamoxifen

Abbreviation: ACEi, angiotensin converting enzyme inhibitor.

potential range of other drug classes that could be used in patients with type 2 diabetes include antihypertensives, the specific use of angiotensin-converting enzyme (ACE) inhibitors or statins for lipid lowering.

2.1.2. Epidemiological definitions

The index disease status in this example is type 2 diabetes mellitus. The other comorbid diseases in this population may include complications such as hypertension and cardiovascular disease, which require drug treatment or other conditions that may influence the index condition, for example, depression [17].

2.1.3. Pharmacoepidemiology definitions

The drugs that are initiated are usually dependent on the severity of presentation, but the index drug therapy for type 2 diabetes mellitus is most often a biguanide (i.e., metformin). The requirement for optimal diabetic control may require the addition of other antidiabetic drugs, such as other oral hypoglycaemics or insulin, that is, multi-index therapies. The codrug therapy in diabetic population may include antihypertensives (i.e., ACE inhibitors), lipid-lowering drugs, and specific drugs indicated for other chronic diseases that impact on the type 2 diabetes. However, there may also be codrug therapy that potentially negatively impacts the index disease under this definition too, for example, steroids in diabetes [18].

2.2. Heart failure with left ventricular systolic dysfunction (LVSD)

2.2.1. Clinical context

There are a range of CVD drugs used in heart failure (HF) with LVSD, with some that are recommended in all patients and others that are indicated and used depending on the clinical severity and comorbidity. Common comorbidity in HF populations includes hypertension (73%), chronic obstructive pulmonary disease (31%), and chronic kidney disease (46%) [19]. Using the American and European national guidance for HF [6,20], there are five CVD drug groups that might be prescribed for HF. Current evidence recommends that both angiotensin converting enzyme inhibitor and beta-receptor blockers are prescribed as first line treatment for all patients with LVSD who do not have other clinical contraindications. The other four drug groups depending on the clinical context and severity include: (i) aldosterone antagonists, (ii) angiotensin-2 receptor antagonists, (iii) vasodilators such as hydralazine and nitrates, and (iv) digoxin. In addition, diuretics are used in all patients as required depending on clinical indication.

2.2.2. Epidemiological definitions

The index disease status in this example is heart failure with LVSD. The other comorbid diseases in this population may include conditions such as atrial fibrillation and ischemic heart disease, which require specific drug

treatments or other conditions that may influence the index condition.

2.2.3. Pharmacoepidemiology definitions

The drugs that are initiated are usually dependent on the severity of presentation, but the index drug therapies for heart failure with LVSD are usually an angiotensin-converting inhibitor (e.g., ramipril) and cardio-selective beta-receptor blocker (e.g., bisoprolol). The requirement for effective symptom control may require the addition of other drugs, such as angiotensin-2 receptor antagonists (ARBs) or diuretics, that is, multi-index drug therapies. The codrug therapy in heart failure with LVSD population may include antihypertensives (e.g., amlodipine), statins and anticoagulants, and specific drugs indicated for other chronic conditions that influence the heart failure status adversely, for example, antidepressants [21].

2.3. The example of breast cancer

2.3.1. Context

There is increasing interest in how the comorbidity status for cancer patients influences outcomes. Examples of common comorbidity in the breast cancer population aged 75 years and over include cardiovascular disease (55%), hypertension (32%), diabetes (32%), COPD (10%), and dementia (7%) [22,23]. Although such evidence is beginning to accrue, the current approaches to treatment are mainly dependent on the type and stage of breast cancer. Yet, there is an absolute necessity for standard definitions as multiple drug treatments in breast cancer change, and on-going treatment creates issues of comorbid disease complications and surveillance safety.

This example provides the ultimate challenge to the pharmacoepidemiology phenotype definition as treatment options are wide-ranging and change over time for the acute and chronic phases. Drugs used in breast cancer now include specific targets (e.g., receptor status determined by genetic risk) with some patients having multiple lines of sequential chemotherapies that may be as a short course or prolonged until there is disease progression [24,25]. Current drug classes cover: (i) combination chemotherapy, (ii) hormone therapy, or (iii) targeted biological therapy, each with their own subclasses. The drug treatment covers initial therapy and the long-term therapy usually through use of hormone drug regimens, as the effectiveness of treatment has led to becoming a chronic ‘‘disease’’ state with increased or normal survival times.

At initiation of treatment, the one chemotherapy agent considered as an option in absence of contraindication, in all breast cancer patients is an anthracycline, often in the form of Epirubicin (in NICE UK guideline) [26]. Other initiating therapies can be tailored to the stage and include E-CMF (epirubicin, cyclophosphamide, methotrexate, and fluorouracil) or FEC (fluorouracil, epirubicin, cyclophosphamide). Another drug class that most patients will have in their chemotherapy is taxanes such as docetaxel or paclitaxel [27]. When and how they are given will depend on the individual patient, for example, nodal involvement will have docetaxel as a part of their adjuvant treatment; paclitaxel tends to be given in metastatic disease, whereas triple receptor negative patients may have carboplatin before any taxane is used.

Some patients may have multiple lines of sequential chemotherapy, such as a short course of taxanes or prolonged treatment until disease progression or toxicities emerge. For metastatic disease, additional interventions include monoclonal agents such as trastuzumab or emtansine [28]. Often when deciding on the next line of therapy, pre-existing toxicities from previous lines of chemotherapies, as well as their comorbidities and drug history are accounted for in the decision-making process.

The breast cancer example illustrates the direct issues between the concepts of comorbidity and multiple drug therapy. Precancer comorbidity influences treatment options as well as the cancer drug treatment subsequently influencing the emergence of other complicating comorbidities. For example, anthracyclines, trastuzumab, and taxanes are responsible for some of the acute and long-term cardiotoxicities, in particular heart failure, and other complications such as liver and renal disease [29]. Other toxicities include bevacizumab, which influences hypertension and capecitabine that is being investigated in triple negative cancers [30], as an alternative or in addition to standard chemotherapy, which influences angina [31]. In terms of potential codrug therapies, these include hormonal treatments such as tamoxifen or anastrozole [32]. These breast cancer treatments on their own create conflict issues with other codrug therapies such as antidepressants, warfarin, or allopurinol [33,34].

2.3.2. Epidemiological definitions

The index status in this example is breast cancer. The other comorbid diseases in this population may include conditions related to drug treatments such as heart, liver, or renal disease or conditions, which affect the index cancer.

2.3.3. Pharmacoepidemiology definitions

The drugs that are initiated are usually dependent on the stage of breast cancer, and usually there are multi-index drug therapies, which are combination of up to several chemotherapies (e.g., epirubicin, cyclophosphamide, methotrexate and fluorouracil or cyclophosphamide, epirubicin and fluorouracil). The requirement for effective symptom control may result in a rapid prescribing cascade, so the codrug therapy in breast cancer population may include symptomatic control (e.g., antiemetics, corticosteroids, iron), as well as specific drugs for other chronic diseases that influence the onset or progression of the cancer or are a consequence of the cancer [35].

However, here, there is an additional distinct concept for defining the use of multiple drugs, which is the distinction between the acute phase treatment and the longer-term

chronic treatment in the breast cancer remission state. In the breast cancer example, index multidrug therapies will be used, but in the longer-term treatment an index follow-up therapy, such as tamoxifen will be used [36]. The cancer example is in contrast to the other diabetes and heart failure example, where drugs once added usually result in a life-long use and are rarely stopped only because of side effects. In breast cancer "chronic disease" scenario, there are distinct and different phases of drug treatment, which balance between the acute proactive drug treatments compared to the potential longer-term preventative treatment.

2.4. A multimorbid patient with type 2 diabetes, LVSD heart failure, and breast cancer

If a patient were to have all three conditions at the same time, the utility of the terminology is further strengthened (Fig. 1). The index multidrug and codrug would combine together to create a separate phenotype, which is multidrug therapy. The multidrug therapy definition would then apply to the combination of any index and codrug therapies and any additional drugs prescribed for specified diseases or conditions. The term does not need to be referenced necessarily to any index condition so that the focus is on the patient taking all their drugs. In the above sections, the focus was on conditions related to index or comorbidity, especially when influences the treatment and outcomes of an index condition. However, as the patient and populations age, other drugs will be added for other conditions, which means that multidrug therapy is the summation of all potential treatments.

A further point is the way in which multidrug therapy occurs. For chronic conditions like diabetes and heart failure, there may be gradual increase in number of drugs, but in cancer, the prescribing cascade may be rapidly turn into multidrug therapy. For conditions such as cancer and heart failure and additional feature may be the initiation of the frailty state [37], which may further increase drug treatments, and the combination of disease and frailty is further associated with adverse outcomes. Consequently an additional term not linked to any condition but all the drugs that a patient uses is total drug therapy.

3. Setting pharmacoepidemiology phenotypes within current evidence on outcomes

The following sections will illustrate how the epidemiological definitions, as applied to the three exemplar conditions, are associated with outcomes. This alignment of phenotypes to outcomes underpins the rationale for the proposed pharmacoepidemiology phenotypes and the importance of a more sensitive definition to describe the prescription of multiple drugs used by patients. Using the proposed definitions, index therapy outcomes relate to improving the prognosis of the index disease and codrug therapy outcomes relate to improvement or worsening of the index disease as well as interactions between the index drug and codrug therapies. Finally, multidrug therapy outcomes focus on patient-centered outcomes and health prioritization.

3.1. Index drug therapy outcomes

For type 2 diabetes, the key initiating drug is often metformin [38,39], and evidence has shown that it is associated

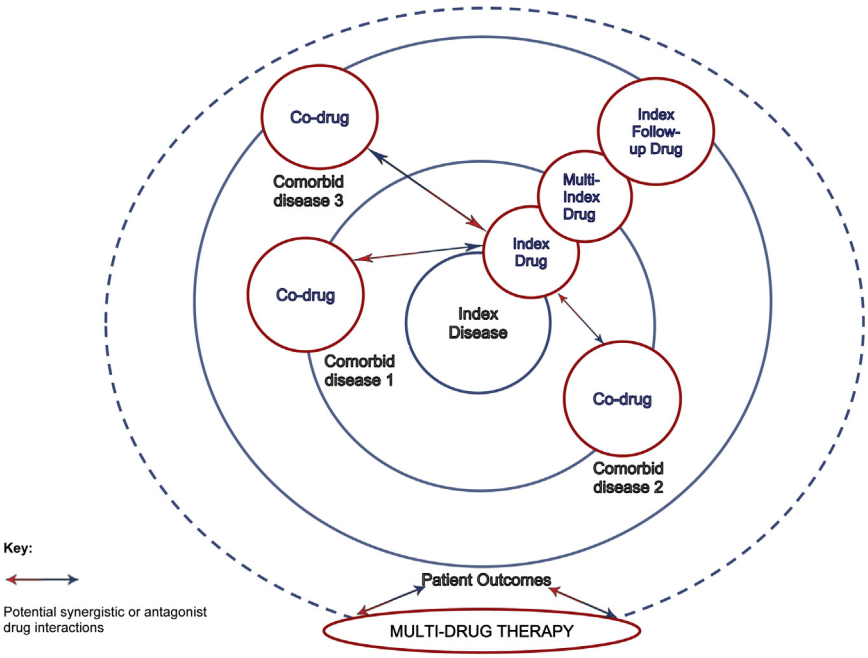

Fig. 1. Conceptual diagram for definitions.

with improved diabetes outcomes and cardiovascular outcomes [40]. Although there are other oral hypoglycemics (sulphonylurea or SGLT2 inhibitors) that may be added to improve control, metformin is still the main indicative drug for T2D. There is evidence that adding sulphonylurea [41] or insulin [42] improves diabetes control but not necessarily the outcomes over long term. Evidence on the long-term benefits of other drug classes, such as glitazones [43] and new SGLT2 inhibitors [44,45], is just emerging, and metformin still remains the first line treatment in current clinical practice.

For heart failure with LVSD, the key initiating drug treatment is with multi-index drug therapies of angiotensin converting enzyme inhibitor and beta-receptor blockers [46]. ACE inhibition reduces overall mortality by 16% to 40%, reduces hospitalizations for asymptomatic HF patients with reduced ejection fraction [47], and improves quality of life [48]. The use of beta-blocker therapy, once considered counterintuitive, is now a standard guideline recommendation, with evidence of a mortality benefit [49].

The evidence on breast cancer combination drug approaches is complex, with no single drug or combinations being the preferred approach, which is dependent on the type of tumor, extent of metastases, and whether it is receptor sensitive [50,51]. The same chemotherapies are also used for other types of cancers, so here the value of terminology relates to logging the primary treatment in medication history with diagnosis.

3.2. Codrug therapy outcomes

The purpose of the codrug therapy definition is that it provides the standard terminology for common drug treatments that impact on the management or prognosis of an index disease. So, for T2D, common codrug therapies such as antihypertensives and statins are important in the prevention of the clinical sequelae of T2D [52,53]. In addition to the beneficial and possible synergistic effects of index and codrug therapies for improving disease outcomes, other codrug therapies may have antagonistic or harmful effects on the index condition or its management. Examples in T2D are the hyperglycemic effects of corticosteroids [54] or the severe and prolonged hypoglycemic effects of some lipid-lowering agents, for example, gemfibrozil, which interfere with the metabolism of some short-acting secretagogues, for example, repaglimide [55]. Conversely overtreatment of the index type 2 diabetes mellitus may also lead to adverse outcomes as in the case of heart failure and mortality outcomes [56].

For HF with LVSD, common cotherapy drugs that might have a beneficial effect on HF outcomes include anticoagulants such as warfarin [57] or anti-arrhythmics such as amiodarone, both prescribed for atrial fibrillation comorbidity [58]. However, other codrug therapies regularly prescribed for other concomitant conditions can have an antagonistic effect on index drug therapies. Clear examples include the sodium and fluid retention and increased systemic vascular resistance associated with nonsteroidal anti-inflammatory drugs (e.g., diclofenac, ibuprofen) and the proarrhythmic effects of antidepressants such as amitriptyline [59,60]. Heart failure is also commonly associated with frailty, and this may also affect the cardiovascular outcomes [61].

For breast cancer, other codrug therapies could include symptomatic control of pain or nausea [62,63], as well as treatment of any complications. However, cancer patients are particularly susceptible to drug interactions particularly in the presence of malnutrition and renal or hepatic dysfunction. A common example of adverse cotherapy is in the increased risk of bleeding from warfarin in the presence of anti-neoplastic agents [64].

All three chronic conditions have a higher risk of comorbid depression, which influences self-care management of the index condition and means that antidepressants often feature as a long-term codrug therapy [65].

3.3. Multidrug therapy outcomes

The above sections show how a patient experiencing just these three conditions will quickly arrive at a multidrug state. The implicit drivers for this phenotype are the single disease guidelines, which promote the use of the individual index drugs or codrug combinations to improve outcomes but also potentially influence adverse outcomes. In aging populations, the number of diseases and associated multidrug therapies increase with a reported 20% of adults older than 65 years prescribed 10 or more medications [66]. Although each individual set of multi-index and codrug therapies have specific benefits, the culmination of such multidrug therapies is associated with adverse outcomes including quality of life, disability, hospital admissions, and mortality [67–69]. Although any drugs without clear indication should be removed, prioritization of remaining disease indicated drug therapies should take account of patient preferences for health goals [70].

4. Discussion

Using the three case examples of chronic illness, which includes the novel implications of cancer, our article proposes and provides the definitions for multiple drug use in patients with multiple chronic illnesses and diseases. It links the use of multiple drug use to the specific terms of comorbidity and multimorbidity and provides the distinct scope of terminology, which is currently not specifically embraced by the term ‘‘polypharmacy’’. The terms it proposes are index drug therapy or multi-index therapies (and index follow on therapy as in the specific case of cancer), codrug therapies, multidrug therapies, and total drug therapy. The importance of clear and standard terminology relates to the chronic disease model [71] in which the goal is on improvement of the clinical outcomes or patient-reported outcomes. Although, drug treatments are one key

component of the multifaceted interventions, which include nondrug therapies, the sole aim and purpose of multiple drug use is to maximize the patient and population benefit and gain the best outcomes.

By proposing clear definitions and terminology and application to the index disease status, comorbidity or multimorbidity, a consistent approach to the clinical and research management can be developed. The benefits of the terminology will be helping clinicians to review potentially harmful multiple drugs by being able to structure them using an organizing principle, for example, an HF specialist might start with the adverse cotherapy drugs, whereas a gerontologist for a frail patient might start on any drugs that do not influence patient important outcomes. The downfall of a vague definition such as ''polypharmacy'' and benefits of the proposed more sensitive definition are potentially in terms of (i) deprescribing—clinicians can perform drug reviews using an organizing principle [72]. This might be looking first at any nonindicated drug therapies followed by harmful cotherapy drugs when managing the index disease, or at patient priorities when managing older frail patients with multidrug therapy when drug−drug interactions are common [73], (ii) scientific rigor—the ability to compare evidence using a more structured and standard definition and measure efficacy of outcomes following drug intervention models and (iii) public health—better understanding of case mix when classifying diseases and drug treatments in populations. Overall the key strength of the new classification is that it enables alignment of conditions with drug interventions, outcomes, and patient priorities.

These definitions also potentially underpin the key scientific concept of the ''polypill'' [74] and the drug typology of interactions, safety, and side effects. Conceptualizing the ''polypill'' as index drug therapies or codrug therapies provides the framework by which dimensions of disease and drugs could be included. Although the ''polypill'' concept uses multiple drug combinations as a potential benefit to patients and populations, the converse problem is that the multimorbidity creates drug−drug interactions and inappropriate prescribing in older populations [75]. Review of current guidelines shows that drug−drug interactions are common and associated with hospitalization, which further supports the characterization of the multidrug phenotype to identify the level and grade of such interactions [76−78]. Other studies have also shown the potential effect on quality of life and patient safety in older populations [79−82]. A recent study on patient safety has suggested there are over 200 medication errors per year in the UK, and adverse drug reactions associated with these could account for several thousand deaths per year [83]. The term ''polypharmacy'' implicitly covers the implications for the patient and population in which drug interventions are a key part of disease prevention and chronic disease management model. It may be assumed by society and by clinical guidelines that polypharmacy is a good thing but really, we do not know that to be the case and will not do until there is a good evidence of how multiple drug use for specific indications is linked with patient outcomes.

The article illustrates through the index case examples, how multiple drug use originates when each disease treatment model is applied, and how that use translates into use of multiple drugs in an individual patient who has, for example, type 2 diabetes, heart failure, and cancer together at the same time. This creates an imperative that standard terminology is employed when trying to understand this field for clinical and research purposes. Arguably, there may be a view that different terminology may be overelaborating the term ''polypharmacy''. Conversely, the alternative and clear view proposed in the article is that it is vitally important to understand the underlying origins of multiple drug use that links single disease drug treatment to multiple disease drug treatment and how that relates to clinical, health care, safety, or patient outcomes.

In conclusion, using three different chronic disease examples, our article proposes the replacement of the term ''polypharmacy''. By linking an index condition with the associated multi-index drug use, to the associated comorbidity conditions with related codrug use to all other nonrelated disease indicated drugs, provides the basis of clearer understanding of the older person with multimorbidity, who has overall ''polypharmacy''. The importance of providing a clear phenotype classification for ''polypharmacy'' enables the key link to the potential mechanisms, such as drug interaction and safety that ultimately relates to the improvement of clinical and health care outcomes in chronic disease management.

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