REVIEW ARTICLE

Polypharmacy—an Upward Trend with Unpredictable Effects

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SUMMARY

Background: Guideline-oriented treatments can lead to polypharmacy, i.e., the simultaneous long-term use of multiple drugs. Polypharmacy mainly affects elderly patients. The goal of this review is to survey the current scientific evidence about polypharmacy, focusing on clinical endpoints, and to point out implications for medical practice and research.

Methods: This selective literature review is based on pertinent publications that were retrieved by a selective search in PubMed employing the terms “polypharmacy AND general practice.” Selected references were considered as well.

Results: In Germany, polypharmacy currently affects approximately 42% of persons over age 65, with an ongoing upward trend. 20–25% of these patients receive potentially inappropriate drugs. Approximately 86% of the daily doses of drugs taken by persons over age 65 are prescribed by general practitioners. There is inconsistent evidence on the question whether polypharmacy affects clinical endpoints such as mortality. It cannot be determined with certainty whether polypharmacy itself, or the underlying multimorbidity, is the reason for worse clinical outcomes. Lists, instruments, and guidelines such as PRISCUS (a list of potentially inappropriate drugs for elderly patients), FORTA (Fit for The Aged), MAI (the Medication Appropriateness Index), and the *Hausärztliche Leitlinie Multimedikation* (a German-language guideline on polypharmacy for general practitioners) can help physicians take care of patients who are taking multiple drugs. It has not yet been proven, however, that their use has any effect on clinical outcomes.

Conclusion: The decision whether to keep giving a drug or to discontinue it must always be made individually on the basis of current treatment goals; drug lists and a pertinent general practitioners' guideline can be useful aids in decision-making. Efforts to pay more attention to multimorbidity and polypharmacy in future studies and guidelines are deserving of support.

► Cite this as:

Moßhammer D, Haumann H, Mörike K, Joos S: Polypharmacy—an upward trend with unpredictable effects. *Dtsch Arztebl Int* 2016; 113: 627–33.
DOI: 10.3238/arztebl.2016.0627

The term polypharmacy is understood to mean long-term consumption of several different drugs at the same time; however, there is no generally accepted definition (1). Many authors describe polypharmacy as the intake of five or more substances, including over-the-counter (OTC) preparations and potentially inadequate medications (PIM) (2). OTC medications can be purchased without a prescription, while PIM are drugs which, when prescribed for the elderly, are associated with an excessive risk of adverse effects in relation to the clinical benefit (3).

The drug-related problems associated with polypharmacy include the following:

- Interactions and side effects,
- insufficient consideration of pharmacokinetics in the elderly, a
- poor adherence or admission to hospital

Moreover, drug–disease interactions (4) may lead to worsening of disease. For example, anticholinergics may adversely affect the course of dementia.

When increasing the number of drugs used in a patient, there is an almost linear association with drug-related problems (5, 6). The proportional distribution of such problems may be the same in patients with more or less than five medications (5). In this light the operationalization of polypharmacy purely according to the number of drugs taken seems unlikely to yield much benefit for routine clinical practice and may even be misleading (5).

Strict adherence to disease-specific guidelines and treatment goals in patients with several chronic illnesses bears the risk of polypharmacy. A systematic investigation showed that simultaneous application of several different guidelines of the National Institute for Health and Care Excellence (NICE) can lead to a large number of drug-related problems (7). Primary care research and population-based studies have yielded heterogeneous findings on the relationship between polypharmacy and clinical endpoints (8).

The aim of this review is to give an overview of recent research into polypharmacy, focusing on medical and particularly general practice activity and on clinical endpoints in Germany, and to outline the resulting implications for research and practice.

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TABLE 1

Lists to ensure adequate pharmacotherapy and to define and avoid potentially inadequate medication in elderly patients

List	Characteristics, structure, presentation	Remarks	Update	Evidence with regard to clinical endpoints
Beers (23) USA, 1991	Negative list (53 PIM) presented by: – organ system – PIM owing to DDI – PIM to be used with particular care – particularly strong anticholinergics	Data on: – reasons for classification as PIM – quality of evidence and strength of recommendation	1997 2003 2012	No intervention study yet carried out
STOPP/START (24, 40) England/Ireland, 2008	Screening tools by organ system and function, classified into: – medications to be discontinued (80 STOPP criteria for PIM) – medications to be used (34 START criteria)	Data on: – reason for classification as STOPP/START criterion – supplemented by information from NICE guidelines	2015	Screening on hospital admission leads to reductions in ADR and length of stay.
PRISCUS (2) (e2) Germany, 2010	Negative list (83 PIM) presented by substance class	– information on concerns, alternatives and measures in the event that the medication has to be continued – information on classification as inadequate medication	2010	– no intervention study yet carried out – randomized study of training intervention in 140 practices ongoing
FORTA (25) (e1) Germany, 2008	List of most frequently used chronic* pharmaceuticals, presented by indication group (e.g., CHD or oncological diseases/solid tumors)	– positive/negative classification on basis of four categories – inclusion of expert commentaries from Delphi process	2012 2014	Intervention study ongoing (400 geriatric inpatients)

PIM, Potentially inadequate medications; DDI, drug-disease or drug-symptom interaction that may exacerbate the disease or syndrome; CHD, coronary heart disease; ADR, adverse drug reaction; NICE, National Institute for Health and Care Excellence

* Taken for more than 4 weeks

Methods

We conducted a selective literature search in PubMed (last update: 6 November 2015) using the search terms “polypharmacy” (5497 hits), “polypharmacotherapy” (68 hits), and “multimедication” (16 hits). To narrow the search, the search term “polypharmacy” was combined with “general practice” (325 hits). All articles published in the year 2000 or later were included. We selected articles from the remaining 299 publications. We also took into consideration references from the selected articles, literature recommendations during the review process, and data from the German Federal Statistical Office (Destatis) and German health insurance providers. The literature selection focused on work from Germany and/or the area of primary care/general practice.

Results

(Pharmaco-)Epidemiology

Around 20% of the German population is above the age of 65 years, and over the next 30 years this will rise to more than 30% (9). Most patients with polypharmacy belong to this age group. According to the Care Provision Report issued by the Scientific Institute (WIdO) of the AOK (a large statutory health insurance provider in Germany), around 42% of persons with statutory health insurance over 65 years of age take five or more drugs; of this group, 20–25% take PIM (10). However, this report does not include medications for which no pre-

scription is required. Similar frequencies for the prescription of PIM are evident in local invoicing data from the AOK Bremen/Bremerhaven and two other health insurance providers, the Techniker Krankenkasse and the Handelskrankenkasse (11).

The PIM prescribed for the over-65s are mostly the following classes of substances (10):

- Cardiovascular drugs (25%)
- Sedatives and sleep-inducing drugs (15%)
- Antiarrhythmics (15%)
- Antidepressants (13%)
- Analgesics/antiphlogistics (9%)
- Antidementives (7%)
- Anticholinergics (6%)

General practitioners prescribe 86% of the daily doses for persons over 65 with statutory health insurance and an estimated 77% of the PIM (10). Patients older than 70 years of age in the care of general practitioners receive an average of 3.7 medications on prescription. Almost 30% of this group receive more than five medications, and 53% receive more than five medications and OTC preparations together (12). Care home residents receive six or seven medications on average (13). Analysis of routinely collected data on patients older than 65 years of age (n = 24 619) from 148 German primary care facilities showed at least one potential drug–disease interaction in around 10% of patients. The risk of such an event increases with the number of diagnoses or syndromes (e.g., heart failure or

syncope) from the Beers list (*Table 1*), the number of medications, and the patient's age (14).

Associations with polypharmacy

It often remains unclear whether polypharmacy has any causal or associative links with the findings in a given patient. Some associations are described in the following.

Multiplicity of health issues: Morbidity and multimorbidity, and therefore the risk of polypharmacy, increase with age (10, 15). Systematic quantification shows that treatment according to the guidelines for diabetes mellitus type 2, heart failure, and depression, together with frequently occurring comorbidities, can be accompanied by a large number of drug-related problems. For example, 32 potentially serious drug–disease interactions have been identified just for treatment of diabetes mellitus type 2, plus 11 frequently occurring comorbidities (7, 16).

A cross-sectional survey of German primary care facilities revealed, for example, that patients with polypharmacy had statistically significantly higher rates of “respiratory distress” (odds ratio [OR] 3.1; 95% confidence interval [2.0; 4.9]), “need for or dependence on auxiliary appliances” (OR 2.6; [1.6; 4.0]), and “poor general condition” (OR 3.5; [2.2; 5.5]) (12).

Sex: Statistics from health insurance providers show no difference between men and women with regard to the mean number of substances prescribed; this has been confirmed in data from general practice (10, 12). According to the above-mentioned Care Provision Report, more women (27%) than men (20%) have PIM prescribed (10).

Mistakes in medication and documentation: Just over three quarters of the patients (n = 382) over the age of 65 years at a Spanish outpatient care center who had been taking more than five medications for a period of more than 5 years stated they had made at least one mistake with their medication in the previous 12 months. The most common errors were incorrect dosage, forgetting to take medications, and confusion among tablets. Mistakes in medication were positively associated with, among other factors, changes in medication, treatment by several different physicians, and difficulty in understanding instructions. There was a negative association with the use of tablet boxes (17). German general practitioners (n = 17) mentioned the following reasons for deviation of medication from the treatment plan (18):

- Incomplete documentation (the primary care physician knows that a patient is taking a certain medication, but does not record it in the file)
- Organizational reasons (medications are documented in the patient's file but not carried over to the treatment plan)
- OTC medications (not documented because they are not subject to prescription or the patient has not mentioned them)
- Prescription by specialists without notification of the general practitioner.

Prescription cascades: Prescription cascades can lead to polypharmacy when adverse effects are treated as symptoms. Examples are prescription of a diuretic to combat edema caused by treatment with amlodipine and prescription of an anticholinergic to deal with urge incontinence following treatment of dementia with an acetylcholinesterase inhibitor (OR 1.55 [1.39; 1.72]) (19, 20).

Undertreatment: Polypharmacy can be associated with undertreatment, i.e., not giving treatment despite indication (e.g., failure to prescribe ACE inhibitors in the presence of systolic heart failure). The likelihood of undertreatment increases with the number of medications already being taken (20, 21).

Lists, instruments, and guidelines

Lists are helpful for dealing with polypharmacy in practice, and instruments are useful for research purposes. For German general practitioners there is also a guideline on multimедication in general practice (*Hausärztliche Leitlinie Multimедikation*), issued by the Leitliniengruppe Hessen, registered with the Association of the Scientific Medical Societies in Germany (AWMF), under the lead of the German College of General Practitioners and Family Physicians (DEGAM) (20).

Lists: *Table 1* gives an overview of lists designed to help ensure appropriate pharmacotherapy and avoid PIM in elderly patients (22). These lists were all initiated or modified in view of the existing evidence on the basis of Delphi processes. The Beers negative list, updated in 2012 (23), is structured by organ system (e.g., cardiovascular system) or therapeutic category (e.g., anticholinergics). For every substance the list supplies the current evidence, the strength of recommendation, and the reasons for classification as a PIM. Furthermore, it lists drug–disease interactions. The STOPP/START list is structured by organ system and represents a practice-oriented screening tool for medications that should be initiated or discontinued (24).

The PRISCUS list and FORTA (Fit for The Aged) were developed for use in the German-speaking countries (2, 25). PRISCUS is a negative list sorted by substance class which also includes medications that are not first-choice drugs in modern pharmacotherapeutic concepts (e.g., phenobarbital and digoxin). Moreover, it includes alternative treatments as well as advice on what to do in the case of a decision in favor of a given PIM. Diseases are also itemized in which the listed drug should not be given. FORTA is structured by indication group (e.g., coronary heart disease). The benefit of a given drug is evaluated in categories from A (This drug has proven indispensable) to D (This drug should be avoided in the elderly).

It has been shown that using the first three of the lists mentioned above documents the prevalence of PIM and reduces the number of different medications consumed (26–28).

TABLE 2

Instruments for assessment and evaluation of medication use (modified from [29])

Instrument	Remarks
ACOVE-3 (Assessing Care Of Vulnerable Elders) (e3–e5)	<ul style="list-style-type: none"> – For very old, frail patients; 392 quality indicators for 26 diseases/situations/symptoms including 24 indicators for prescription and use of medications – Studies with pharmacists to compare various instruments for detection of PIM and PPO
MAI (Medication Appropriateness Index) (20), (e6)	<ul style="list-style-type: none"> – Instrument recommended for use in primary care with 10 (modified: 14) yes/no questions on indication, evidence, dosage, safety of use, etc. – Frequently used research instrument
GPGP-algorithm (Good Palliative-Geriatric Practice Algorithm) (32)	<ul style="list-style-type: none"> – Yes/no algorithm on evidence, indication, symptoms, adverse effects, etc. – Initially developed for screening of aged patients in care homes
SMOG (Screening Medications in the Older Drug User) (e7)	<ul style="list-style-type: none"> – No detailed information available on structure of instrument – Controlled intervention study involving pharmacists with 87 patients per group; 16% reduction in medication-related problems
ARMOR (Assess, Review, Minimize, Optimize, Reassess) (e8)	<ul style="list-style-type: none"> – Assess: elevated risk of ADR according to Beers list; Review: interactions, drug-disease interaction, general condition, etc.; Minimize: unnecessary medications, medications with no evidence, etc.; Optimize: duplication, redundancy, renal function etc.; Reassess: vital parameters etc. – Instrument used by pharmacists; no study carried out to date
TIMER (Tool to Improve Medications in the Elderly via Review) (e9)	<ul style="list-style-type: none"> – Four areas: safety, adherence, economy, and treatment goals – Study on recognition of medication-related disorders by pharmacists and students in typical cases; yet to be tried in clinical practice
AOU (Assessment of Underutilization) (e10)	<ul style="list-style-type: none"> – By category: “no underprescription”; “medication discontinued due to, for example, patient preference or adverse effects”; “definite underprescription” – Cross-sectional study on prevalence of underprescription in elderly multimorbid patients on discharge from hospital

PIM, Potentially inadequate medication; PPO, potential prescribing omission; ADR, adverse drug reaction

Instruments: *Table 2* lists the instruments in current use for assessment of drug consumption, particularly for purposes of research (29).

Guidelines: The above-mentioned guideline on multimедication takes account of practice-relevant lists (PRISCUS, STOPP/START, Beers) and the instrument MAI (Medication Appropriateness Index). The latter contains, for example, summaries of drug interactions, QTc-lengthening medications, and substances associated with an increased risk of falls.

Evidence on clinical endpoints

The evidence on clinical endpoints (*Table 3*) is heterogeneous (8). In particular, the effect of interventions (e.g., the use of lists; see *Table 1*) regarding clinical endpoints remains to be demonstrated (28).

A Cochrane review of 12 randomized controlled trials (RCTs) with complex interventions (use of lists and instruments by pharmacists or physicians) showed in some cases ($n = 2$) reduction of the MAI score or the number of medications from the Beers list. The effects with regard to the clinical endpoints “hospital admission” ($n = 5$) or “drug-related problems” ($n = 6$) were heterogeneous. Overall, the authors of the review classify the evidence quality of the results as low to very low (28).

A systematic review published in 2014 covered 50 population-related observational studies of outpatients. The authors investigated the associations between number of medications and clinical endpoints (*Table 3*). The severity of morbidity was taken into account. The results were inconsistent with regard to the various endpoints, the findings within the same endpoints, and mortality. The authors' conclusion was that the results only partly supported the hypothesis that polypharmacy per se constitutes a risk factor for undesired clinical endpoints (8).

One RCT with 259 care home residents (≥ 65 years old) described a medication check by a clinical pharmacist. The following endpoints were reduced over the course of follow-up (6–12 weeks): “unnecessary therapeutic duplication” (in 47 of every 100 patients; 95% CI [20; 74]) and “problems with cardiovascular pharmacotherapy” (in 37 of every 100 patients; 95% CI [9; 66]). No improvement was seen for “psychotropic medication” or “nonsteroidal antiinflammatory drugs in patients at high risk of complications from peptic ulcers” (30).

In a study of 70 outpatients of advanced age (average 83 years) published in 2010, Garfinkel et al. reduced the number of medications according to the GPGP-algorithm (*Table 2*) (31). The study had no control group; the mean duration of follow-up

was 19 months. On average, four to five medications could be discontinued. Almost all of the patients reported a general improvement in their state of health. However, 2% of the discontinued medications were reindicated during the follow-up period and prescribed again. The authors concluded that the number of medications taken by the elderly can be reduced (31). An earlier non-randomized study by the same group, published in 2007, investigated reduction of the number of medications according to the GPGP-algorithm in 119 care home residents of advanced age. In the control group (n = 71), no reduction of medications took place. After follow-up for 1 year, mortality was statistically significantly higher in the control group (45% versus 21%) (32). A systematic review of RCTs and high-quality observational studies in patients over 65 years of age showed that with appropriate information and monitoring, antihypertensives and psychotropic substances (neuroleptics, benzodiazepines, antidepressants) could be discontinued without harm (in terms of falls, cognitive function, and psychomotor function) in 20 to 100% of selected patients (33).

Discussion

Polypharmacy is common in elderly patients. Especially general practitioners are often confronted with this challenge (10). Polypharmacy is always part of a complex scenario with multiple relations (causal and/or associative). To cope with this complexity, lists, instruments, and guidelines have been developed for assessment of polypharmacy. The obvious question is whether their use improves the clinically relevant endpoints. Owing to the lack of sufficient evidence no conclusive answer can yet be given. A further question is whether worsened clinical endpoints result from polypharmacy itself or rather from the underlying multimorbidity in patients taking multiple medications. And, as Fried et al. ask, is it even feasible that reducing the number of medications can achieve an improvement in clinically relevant endpoints (8)? These questions cannot be answered conclusively on the basis of the currently available evidence from systematic reviews and individual studies (8, 28, 31). Nevertheless, there are implications for research and for daily practice.

Implications for research

Research has shown that the use of lists and instruments can help to identify PIM. Future studies will have to pay attention to both sociodemographic characteristics (age, education level) and health care system-related factors (e.g., parallel treatment by specialists, frequent changes of treating physician). Furthermore, the target population (for instance patients being treated according to one or multiple guidelines, or the nature and severity of the morbidity) must also be properly considered.

TABLE 3

Examples of maximal, positive and statistically significant associations of clinical endpoints with polypharmacy in cohort studies*¹ (≥ 4 medications) (8)

Clinical endpoint	Odds ratio [95% CI]
Falls	1.06 [1.02; 1.09] 1.22 [1.04; 1.43] 1.6 [1.1; 2.1]
Fall-associated variables	
– dizziness	1.80 [1.02; 3.19] 1.6 [1.1; 2.3]
– fear of falling	no data* ²
– fractures	no data* ²
Adverse drug reactions	1.34 [1.1; 1.63] 3.61 [1.92; 6.78]
Hospitalization rate	1.04 [1.03; 1.06]
Mortality rate	1.04 [1.00; 1.07] 1.09 [1.04; 1.15]
General health	Weight loss: 2.78 [1.38; 5.60] ADL: 1.95 [1.54; 2.46]
Cognitive performance	Dementia: 1.34 [1.23; 1.46]

*¹ Cohort studies with good quality of adaptation to chronic diseases

*² No data for association from cohort studies with good quality of adaptation to chronic diseases
ADL, Activities of daily life; 95% CI, 95% confidence interval

Clinical endpoints should be chosen with regard to their relevance in the population concerned. As suggested by Muth et al. (34), one of the endpoints in primary care could be quality of life. It would also be desirable to include endpoints relevant to the patients' lives, such as aspects of self-management (35).

Implications for daily practice

The decision-making aids presented here (Tables 1 and 2) have not yet been validated with regard to meaningful clinical endpoints. Structured medication checks can identify specific drug-related problems. Online applications can be used for this purpose (e.g., Epocrates or Medscape for drug interactions or www.dosing.de for advice on dosage).

Age-specific changes, e.g., in renal function and cognitive status, must be taken into consideration, as must the patient's social circumstances and risk of falls. The use of one single medication plan and of tablet boxes should be promoted. As part of its initiative for drug treatment safety (*Initiative zur Arzneimitteltherapiesicherheit*), the German Federal Ministry of Health has developed a proposal for a uniform medication plan to be used nationwide. This document lists the indications, dosage, and instructions on intake for all prescription drugs and OTC preparations the patient is using (36).

The decision to continue or discontinue medications should always be guided by the individual treatment goals, particularly improvement of the

prognosis, prevention of worsening of disease, and/or symptom control. Patients and their relatives very much appreciate it when changes in medication are discussed with them (37).

Future guidelines should take greater account of drug interactions, medications that may make existing diseases worse, and comorbidities (7). Systematic analyses show that evidence-based guidelines are of only limited application in multimorbid patients unless they were developed specially with this group in mind and specifically address their treatment (16, 38).

More attention to the development of guidelines in electronic form could help make it easier to detect potential medication-related problems (1). A recent cohort study of 8578 persons over 65 years of age showed that coexisting diseases exert a crucial influence on the benefit of certain pharmacotherapeutics (39).

Efforts to deepen our understanding of multimorbidity and polypharmacy through studies and guidelines merit support.

Conflict of interest statement

Dr. Mörike has received reimbursement of travel costs from Berlin-Chemie. The remaining authors declare that no conflict of interest exists.

Manuscript submitted on 25 November 2015, revised version accepted on 6 June 2016

Translated from the original German by David Roseveare.

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KEY MESSAGES

- Consistent adherence to treatment guidelines potentially leads to polypharmacy.
- Polypharmacy mainly—and increasingly—affects the elderly. General practitioners prescribe almost 90% of the daily doses consumed by patients over 65 with statutory health insurance in Germany.
- Lists, instruments, and guidelines, such as the PRISCUS, Beers, and STOPP/START lists, MAI and FORTA, and the guideline on multimorbidity in general practice, may be helpful in carrying out a structured medication check.
- The currently available evidence does not demonstrate with certainty whether structured interventions (e.g., a medication check) can exert any influence on clinically relevant endpoints (e.g., morbidity, falls) in patients with polypharmacy.
- The currently available evidence from systematic reviews and individual studies does not permit firm conclusions as to whether polypharmacy itself or rather the underlying multimorbidity in patients taking multiple medications is responsible for the poorer outcomes with regard to clinical endpoints.

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Supplementary material to:

Polypharmacy—an Upward Trend with Unpredictable Effects

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Dtsch Arztebl Int 2016; 113: 627–33. DOI: 10.3238/arztebl.2016.0627

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