Identifying High-Risk Medication Prescriptions to Prevent Potentially Severe Adverse Drug Events in Primary-Care Patients with Chronic Multimorbidities: The Polychrome Study

Running title: Preventing Adverse Drug Events Associated with Polypharmacy

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Abstract: Background: The association between multimorbidities and polypharmacy among elderly individuals is well documented, and polypharmacy has been shown to increase the risk of adverse drug events (ADEs). However, little information is available about the risks associated with the lifelong use of medications to treat chronic multimorbidities. Objective: To determine the prevalence and nature of high-risk prescriptions among primary-care patients with chronic multimorbidities. Methods: We studied a weighted stratified random sample of 105 prescriptions for different patients with chronic multimorbidities taken from the Polychrome database established using information from the French primary-care record database (Observatoire de la Médecine Générale). A medication review was conducted to identify contra-indications and potential drug-drug interactions for each prescription. Results: Contra-indications were identified for 60 (57.1%) prescriptions, potential drug-drug interactions for 70 (66.7%), absolute contra-indications for 9 (8.6%), and inadvisable drug combinations for 11 (10.5%). In all, 19 (18.1%) different patients were at risk for major ADEs. Cardiovascular and nervous-system drugs contributed 66.2% of contra-indications and 69.3% of potential drug-drug interactions. Conclusions: This exploratory study confirms the high prevalence and potential seriousness of prescriptions at risk for ADEs in a population of primary-care patients with chronic multimorbidities. The high prevalence of interactions involving the cardiovascular and nervous systems indicates that efforts to improve prescription practices should target these two categories of conditions and drugs in patients with chronic multimorbidities.

Key words: Primary care, General practice, Chronic disease, Pharmacotherapy management, Drug-drug interactions, Medication review.

1. Background

Among patients seen by general practitioners (GPs), some have multiple risk factors and/or multiple comorbidities requiring the concomitant use of several medications [1, 2]. In patients with chronic multimorbidities, polypharmacy is difficult to avoid and constitutes a major public health issue,
particularly among older individuals [3, 4]. Polypharmacy is associated with five major problems: an increased number of inappropriate treatments, an increased risk of potentially dangerous drug-drug interactions, an increased risk of contra-indications due to the concomitant presence of several morbidities, decreased treatment adherence by the patients, and increased healthcare costs. To better manage the human and economic aspects of polypharmacy, the underlying multimorbidities and patient behaviours must be characterised, as they must be taken into account when evaluating the risk of adverse drug events (ADEs), as well as critical trade-offs [5, 6].

The association between multimorbidities and polypharmacy among elderly individuals is well documented, and polypharmacy has been shown to increase the risk of ADEs [7-9]. However, little information is available about the risks associated with the lifelong use of medications to treat chronic multimorbidities. France does not have a system ensuring the continuous and exhaustive recording of reasons for GP visits. Consequently, the prevalence and characteristics of primary-care patients with chronic multimorbidities requiring polypharmacy are not well known. Pharmacovigilance is challenging in patients with multimorbidities, and few data on high-risk medication prescriptions in primary-care patients in France have been published. Case ascertainment has relied on reporting by GPs and on patient admissions for serious ADEs [10].

The Polychrome research project conducted by our group had three parts: the first consists in characterising the nature of the most common clusters of chronic conditions and medications in patients with chronic multimorbidities seen by GPs in France [11], the second in identifying the pharmacological risks with the goal of optimising prescriptions [12], and the third in assessing determinants of polypharmacy based on six focus groups of 10 GPs [13].

Here, our objective was to determine the prevalence of prescriptions involving a risk of ADEs, as well as the nature of the risk, in primary-care patients receiving chronic polypharmacy to treat multimorbidities. We sought to identify common and potentially serious risks that were amenable to immediate improvement via interventions targeting GPs.

2. Methods

2.1 Selection of Prescriptions

The data used for this study were obtained from the data warehouse developed by the French Society for Primary Care (Société Française de Médecine Générale, SFMG) using information supplied by a network of GPs (Observatoire de la Médecine Générale, OMG) [14]. All GPs in the network use a manual of standardised diagnoses (Dictionnaire des Résultats de Consultation, DRC) to complete electronic medical records for their patients. The manual comprises both 277 (International Classification of Diseases) ICD10-coded definitions that account for 95% of health problems managed in primary care and a medication database that serves as a prescription-writing aid. As of May 2007, the OMG data warehouse had 153 GPs, 646,000 patients, 5.6 million visits, 7.6 million identified health issues, and 4.3 million prescriptions with 13 million medications prescribed.

For the Polychrome research project, we built a specific database using information entered into the OMG data warehouse in 2002-2004. Patients with at least one chronic condition in 2002 and 2003 and at least one visit in each of the 3 consecutive years from 2002 to 2004 were selected. The sample was composed of 45,018 patients [25,094 (55.74%) females], 284,126 visits, 718,772 chronic conditions, and 242,879 prescriptions with 1,471,678 prescribed medications. Of the six chronic multimorbidity patterns identified in this sample (Figure 1) [11], the four most prevalent were selected for the present study (patterns 1 to 4 in Figure 1).
After discussion with pharmacologists, we determined that 100 prescriptions provided a reasonable balance between work feasibility and result consistency. We considered only prescriptions for at least five concomitant medications (five was the median number of medications per prescription in the entire Polychrome database). We took a weighted stratified random sample of at least 100 prescriptions for different patients having one of the four chronic multimorbidity patterns selected for the study. To control for the potential influence of gender and age on our results, we used two stratification variables, gender and age group (26-39 years, 40-59 years, 60-69 years, 70-79 years, and ≥80 years). To ensure that the distribution of the prescriptions matched that of the four multimorbidity patterns, 40% of prescriptions were taken from pattern 1, 20% from pattern 2, 15% from pattern 3, and 25% from pattern 4. Once the prescriptions were selected, disease durations and prescribed medications were retrieved from the Polychrome database. Five prescriptions were for patients who already had another prescription selected and were therefore excluded from the study. This left 105 prescriptions for 105 different patients (flow chart in Figure 1).

2.2 Pharmacological Analysis

The prescriptions were analysed using digital versions of the French drug compendium [Vidal dictionary] for 2002, 2003, and 2004 and of the drug-drug interaction booklet (http://vidalubmmedica.com/solutions/vidal-integrated) for 2002 and 2003; no version of this booklet was published in 2004, which was a transition period before the publication of a medicines compendium developed by the French Agency for Healthcare Product Safety [ANSM].

The pharmacological analysis was conducted by drug and therapeutic class and not by prescription. First, the Vidal and interaction booklet information on the medication was reviewed for each year of the study period. Important items of information were available in the drug compendium [Vidal] monographs, such as precautions required in patients with renal dysfunction, some of which were also discussed in the ‘Dosage’ or ‘Pharmacokinetics’ section of the monographs. Then, the contra-indications and potential drug-drug interactions were identified for each prescription that included that medication.

Identified contra-indications [potential interactions between a prescribed medication and a health condition] were collected for each patient and classified into four groups as follows: absolute contra-indication, relative contra-indication, warning required, and precautions required. Identified potential drug-drug interactions [interactions between two drugs in the prescription] were collected for each patient and classified into four groups: contra-indicated drug combination, inadvisable combination, precautions required, and special consideration required.

The study data were handled confidentially in compliance with the Commission Nationale de l’Informatique et Liberté (CNIL, approval #311668). The data were managed using ACCESS® [Microsoft, Redmond, WA, USA] and statistical tests performed using SAS 9.1® [SAS Institute Inc., Cary, NC, USA].

3. Results

The prescriptions included in the study were for 105 patients with chronic multimorbidities including 55 (52.4%) females and 50 (47.6%) males, aged 34 to 95 years (median, 71 years). The prescriptions were for 676 medications designed to treat 528 chronic conditions. The median number of chronic conditions discussed during each visit was 5 [range, 2-13] and the median number of medications per prescription was 7 [range, 3-21]. Table 1 reports the distribution of the prescribed medications according to the first level of the Anatomical Therapeutic Chemical [ATC] Classification System.
Fig. 1 Flow chart of prescriptions selection.

OMG / SFMG data warehouse, 1993 to May 2007
153 GPs - 646 000 patients
5.6 millions visits – 4.3 million prescriptions
7.6 million health conditions treated - 13 million medications prescribed

Polychrome database, 2002-2004
68 GPs - 45 018 patients with chronic conditions
284 126 visits – 242 879 prescriptions
718 772 health conditions treated - 1 471 678 medications prescribed

Selection of patients having at least
- One chronic condition treated in 2002-2003
- One visit in 2002, 2003, and 2004

Typological analysis of chronic conditions
Multiple correspondence analysis
+ Ascending hierarchical classification

| Pattern (%) | 1 (37.8) | 2 (23.1) | 3 (14.3) | 4 (13.4) | 5 (7.5) | 6 (3.9) |
|-------------|----------|----------|----------|----------|---------|--------|
| Main systems involved and age group |
| Cardiovascular disease |
| Musculo-skeletal disease >60 years |
| Hypertension |
| Hyperlipidaemia |
| Coronary artery disease |
| Example of comorbidities |
| Widely variable diseases |
| Females >70 years |
| Osteoarthritis |
| Varicose veins |
| Coronary artery disease |
| ACE inhibitor |
| Cholesterol-lowering agent Beta-blocker |
| Anti-thrombotic agent |
| Example of concomitant medications |
| Analgesic |
| Vasodilator |
| Beta-blocker |
| Anti-thrombotic agent |
| NSAID |
| Analgesic |
| Anti-depressant |
| Muscle relaxant |
| Beta-blocker |
| Cholesterol-lowering agent |
| Anti-anxiety agent |

Random sample of prescriptions stratified on patient gender and age group
Sampling rates: 40% Pattern 1, 20% Pattern 2, 15% Pattern 3, 25% Pattern 4

105 prescriptions studied
53 GPs - 105 Patients / visits
528 treated health conditions - 676 medications prescribed
3.1 Contra-indications and Potential Drug-drug Interactions

Contra-indications and/or potential drug-drug interactions were identified for nearly two-thirds of the 105 prescriptions.

The 155 contra-indications identified in this study occurred for 22.8% of prescribed medications and 29.2% of chronic multimorbidities. Of the 26 different chronic multimorbidities for which contra-indications were identified, 7 accounted for 79.1% of all contra-indications: coronary artery disease (24.0%), type 2 diabetes (18.8%), hypertension (11.0%), chronic congestive heart failure (9.7%), renal failure (6.5%), lower-limb peripheral arterial disease (5.2%), and atrial fibrillation (3.9%). Contra-indications were identified for 25 different medications, and 78.5% of them were ascribable to three drug classes: cardiovascular system (51.9%), nervous system (14.3%), and respiratory system (12.3%) [Table 2]. In 54% of cases, the contra-indications involved the following drugs, by order of decreasing frequency: angiotensin-converting enzyme (ACE) inhibitors, inhaled beta-agonists, angiotensin II receptor antagonists, non-steroidal anti-inflammatory drugs (NSAIDs), anti-depressants, and oral anti-diabetic agents.

We identified 197 potential drug-drug interactions, involving 58.3% of prescribed medications and 45 different medications. Three drug classes accounted for 80.5% of potential drug-drug interactions: cardiovascular system [36.3%], nervous system [33.0%], and alimentary tract/metabolism [11.2%]. Among potential drug-drug interactions, 49.2% involved two drugs in either the cardiovascular system class or the nervous-system class [Table 3]. Potential drug-drug interactions were related in 60% of cases to the following types of drugs, by order of decreasing frequency: beta-blockers, anti-anxiety agents, anti-depressants, opioids, loop diuretics, ACE inhibitors, oral anti-diabetic agents, NSAIDs, and anti-thrombotic agents.

Table 1  Distribution of the prescribed medications in the 105 prescriptions according to first-level ATC codes.

| ATC level-1 code                  | Medications [n = 676] | Number | %  |
|-----------------------------------|-----------------------|--------|----|
| Cardiovascular system [C]         |                       | 212    | 31.4|
| Nervous system [N]                |                       | 153    | 22.6|
| Alimentary tract/metabolism [A]   |                       | 150    | 22.2|
| Musculo-skeletal system [M]       |                       | 38     | 5.6 |
| Respiratory system [R]            |                       | 36     | 5.3 |
| Blood and blood-forming organs [B]|                       | 30     | 4.5 |
| Various                           |                       | 57     | 8.4 |

Table 2  Distribution of contra-indications according to ICD10 chapters and first-level ATC codes

| ICD-10 chapters                      | First-level ATC codes | A | B | C | G | H | M | N | R | Total |
|--------------------------------------|-----------------------|---|---|---|---|---|---|---|---|-------|
| Diseases of the circulatory system   |                       | 5 | 1 | 48| 6 | 6 | 5 | 7 | 13  | 91    |
| Diseases of the digestive system     |                       |   |   |   |   |   |   |   | 2  | 4     |
| Diseases of the genito-urinary system|                       | 3 | 4 |   |   | 5 |   |   | 12  |       |
| Diseases of the respiratory system   |                       | 1 |   |   |   |   | 1 |   | 2   |       |
| Diseases of the musculo-skeletal system|                     |   |   |   |   |   |   |   | 1   | 1     |
| Endocrine, nutritional, and metabolic diseases|                       | 2 | 27| 1 | 1 |   | 3 | 3 | 37  |       |
| Symptoms, signs, and abnormal clinical and laboratory findings | | 1 |   |   |   |   | 1 | 1 | 3   |       |
| Mental and behavioural disorders     |                       | 1 |   |   |   |   |   | 1 | 2   |       |
| Total                                |                       | 10| 2 | 80| 7 | 7 | 7 | 22| 19  | 154   |
Table 3  Distribution of potential drug-drug interactions according to first-level ATC codes.

| First-level ATC codes                | A  | B  | C  | G  | H  | M  | N  | R  | S  | Total |
|--------------------------------------|----|----|----|----|----|----|----|----|----|--------|
| A Alimentary tract and metabolism    | 2  |    |    |    |    |    |    |    |    | 2      |
| B Blood and blood-forming organs     | 3  | 4  |    |    |    |    |    |    |    | 7      |
| C Cardiovascular system              | 30 | 1  | 40 |    |    |    |    |    |    | 71     |
| G Genito-urinary system              |    |    |    | 4  |    |    |    |    |    | 4      |
| H Systemic hormonal preparations     | 1  | 5  | 6  |    |    |    |    |    |    | 12     |
| M Musculo-skeletal system            | 1  | 7  |    |    | 10 |    |    |    |    | 18     |
| N Nervous system                     | 3  | 10 |    | 57 |    |    |    |    |    | 73     |
| R Respiratory system                 | 5  |    | 1  |    |    |    |    | 2  |    | 8      |
| S Sensory organs                     |    | 1  |    |    | 1  |    |    |    |    | 2      |
| Total                                | 42 | 20 | 72 | 0  | 0  | 4  | 57 | 2  | 0  | 197    |

3.2 Absolute Contra-indications and Inadvisable Drug Combinations

The nine medications for which absolute contra-indications were identified accounted for 1.3% of prescribed medications and the 11 inadvisable drug combinations for 3.3% of prescribed medications. We identified no contra-indicated drug combinations.

Of the nine absolute contra-indications, seven involved cardiovascular disease, one renal failure, and one respiratory failure. The medications involved were beta-blockers in patients with peripheral vascular disease [lower-limb peripheral arterial disease or Raynaud’s phenomenon], a step 2 analgesic agent with an oral anti-diabetic agent in a patient with coronary artery disease, and menopausal hormone replacement therapy in a patient with hypertension.

Of the 11 inadvisable drug combinations, nine involved cardiovascular medications: an angiotensin II receptor antagonist was prescribed with potassium or a potassium-sparing diuretic agent in six cases, an ACE inhibitor with a potassium-sparing diuretic agent in one case, and a selective calcium-channel blocker with a beta-blocker in two cases. The remaining two combinations consisted in aspirin with either an NSAID or an oral vitamin K antagonist.

3.3 Prevalence of Iatrogenic Potential and Influence of Patient Characteristics

Of the 105 patients with chronic multimorbidities, 60 (57.1%) had contra-indications and 70 (66.7%) potential drug-drug interactions. These prevalences increased with age from nearly 50% in patients aged 40 to 69 years to nearly 80% in those aged 80 years or over.

The 9 (8.6%) patients with absolute contra-indications and 11 (10.5%) patients with inadvisable drug combinations were evenly distributed among the age groups. In one patient, both a contra-indication and an inadvisable drug combination were identified. Thus, in all 19 (18.1%) different patients were at risk for potentially serious ADEs. No difference was found between males and females regarding the degree of seriousness of potential ADEs.

4. Conclusions

The results of this exploratory study indicate that both the prevalence and the potential seriousness of prescribing errors are high in primary-care patients with chronic multimorbidities. High-risk prescriptions were identified for more than half the patients. More importantly, absolute contra-indications or inadvisable drug combinations were identified in nearly one-fifth of patients, who were consequently at risk for serious ADEs. Contra-indications were identified for nearly one-third of the chronic conditions and medications, and two-thirds of contra-indications involved cardiovascular conditions. Potential drug-drug interactions were found for more than half the prescribed medications, and two-thirds of potential drug-drug interactions involved cardiovascular and nervous-system drugs. Among contra-indications and
potential drug-drug interactions, less than 6% involved a risk of serious ADEs [absolute contra-indication or inadvisable drug combination]. These high-risk errors occurred chiefly for cardiovascular conditions and drugs. The high prevalence of interactions involving the cardiovascular and nervous systems, together with the substantial proportion of patients having cardiovascular and/or nervous-system diseases, indicates that efforts to improve prescription practices should target these two categories of conditions and drugs in patients with chronic multimorbidities.

Our finding that high-risk medication prescriptions are common in primary care is consistent with previous studies. A prospective cohort study was conducted in the United States in 2000 in 661 patients older than 18 years who had received at least one prescription at one of four adult primary-care practices. Among them, 25% had ADEs and 3% serious ADEs[15]. Another prospective cohort study conducted in the United States in 2005 in individuals older than 18 years included 157 patients seen at a family medicine residency clinic. A risk of ADEs was identified for 32% of prescriptions 16]. This prevalence is only about half that found in our study, probably because we included only patients with chronic multimorbidities. Moreover, our finding of common drug-drug interactions involving cardiovascular and nervous-system drugs is consistent with a retrospective Swedish study carried out in 2008 in 4970 adults selected at random from the general population, of whom 12% had a history of ADEs. Among these ADEs, drug-drug interactions involved cardiovascular drugs in 29.6% and nervous-system drugs in 19.8% of cases [17]. Studies that measured the prevalence and seriousness of prescription errors involving contra-indications or potential drug-drug interactions produced widely variable results [8, 9, 17]. These discrepancies may be ascribable to a number of factors such as cultural prescription habits, the drug information reference used, and the study characteristics. The increase in the risk of potential ADEs with advancing age is consistent with earlier work: as age increases, the numbers of chronic conditions and medications increase also, leading to a higher risk of iatrogenic events [18-20]. The prevalence of potentially serious prescription errors in our population was similar to that found in a study of all individuals covered by the statutory healthcare system in a district of south-western France [Languedoc-Roussillon] [21].

A recent review showed that most of the studies of ADEs focussed on hospitals [22]. In France, data are scarce on drug-prescription quality in primary care. In this study, we used an exploratory approach designed to provide a systematic and exhaustive description of prescription errors carrying a risk of ADEs and made during real-life primary-care visits. We did not seek to identify pre-defined contra-indications or potential interactions. Given our focus on chronic multimorbidities and chronic polypharmacy, we weighted our sample of prescriptions towards the older age groups, with over two-thirds of included patients being older than 60 years. The database used (OMG) is the only large French primary-care database that systematically records diagnoses and medications using standardised terms. It has been too rarely used for pharmacotherapy analyses. Electronic prescription with prescription-checking software is now widely used among GPs in France. We therefore investigated this system, rather than handwritten prescriptions, which may carry a higher risk of ADEs. The working conditions of GPs in France have not changed since the data collection period (2002-2004). Although the French National Authority for Health (HAS) created a label for prescription-checking software in 2012, computer alarms remain based on medicine compendiums, as opposed to clinical data. Furthermore, a systematic review suggests that drug-interaction software may have no impact in hospitals or primary care [23]. Except for the dextropropoxyphene-paracetamol combination, the
drugs identified in interactions and contra-indications in our study are still used today. A limitation of our study is that only two types of inappropriate prescription were studied (contra-indications and drug-drug interactions). In particular, we did not evaluate data on therapeutic indication, effectiveness, dosage, or distribution over 24 hours, which may show room for improvement in primary care [12].

When prescribing medications to patients with multiple chronic conditions, GPs must take into account the medications prescribed by other physicians in hospitals or by specialists in private practice. Interventions designed to provide information, education, and new organisation models to physicians must target all these prescribers [24]. The curriculum for the last few years of medical school should include information on the management of patients with chronic multimorbidities [who receive relatively little attention in the current French curriculum] and on the specific challenges raised by the need to use multiple medications in the same patient [25]. Emphasis should also be put on the optimal handling by GPs of chronic prescriptions over time, in collaboration with pharmacists [26, 27]. Patients need information, education, and support to encourage non-pharmacological risk-factor control, particularly regarding cardiovascular risk factors. Finally, clinical practice guidelines need to be improved, as they focus chiefly on health issues considered in isolation, despite several recent improvements regarding the specific patient populations seen by GPs [28].

The risks associated with medication use are substantial in patients who have chronic multimorbidities and are partly unavoidable given the vast number of interactions that can occur with each drug. Prescription errors associated with potentially serious ADEs occurred in about one-fifth of our patients, an unacceptably high rate. A number of tools are available to GPs, although currently available software remains less than ideal. Medications targeting the cardiovascular and nervous systems should receive special attention.

5. Declarations / Acknowledgements

Ethical approvals

The study data were handled confidentially in compliance with the requirements of the French Data Protection Agency (Commission National de l’Informatique et des Libertés, CNIL, approval #311668).

Funding

This study received financial support from the publicly funded teachers’ health insurance agencyMGEN and the French National Authority for Health (HAS).

Role of the Sponsor: The funding source had no role in the study design; collection, analysis, or interpretation of data; writing of the manuscript; or decision to submit the manuscript for publication. The researchers were independent from the funding source.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Acknowledgements

The authors are indebted to AWolfe MD for her helpful review of the manuscript.

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