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ORIGINAL ARTICLE

Risk factors for potential drug interactions in general practice

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Abstract

Objective: To identify patient- and practice-related factors associated with potential drug interactions. *Methods:* A register analysis study in general practices in the county of Funen, Denmark. Prescription data were retrieved from a population-based prescription database (Odense University Pharmacoepidemiologic Database, OPED) covering prescriptions to all inhabitants in the county of Funen, Denmark. All individuals exposed to concurrent use of two or more drugs (polypharmacy) were identified. Combinations of drugs with potential interactions were registered and classified as major, moderate, or minor, depending on the severity of outcome and the quality of documentation. A two-level random coefficient logistic regression model was used to investigate factors related to potential drug interactions. *Results:* One-third of the population was exposed to polypharmacy, and 6% were exposed to potential drug interactions during 1 year. Patient factors associated with increased risk of potential drug interactions were high age, a high number of concurrently used drugs, and a high number of prescribers. Practice factors associated with potential drug interactions were a high percentage of elderly patients and a low percentage of female patients listed.

Conclusion: Prescription data may be useful in quality-improvement programmes to identify groups of patients and practices at increased risk of drug interactions.

Key words: *Drug interactions, polypharmacy, practice variation*

Introduction

It has been estimated that 10–20% of hospital admissions are caused by drug-related events, and about 1% are caused by drug interactions (1). In some studies, drug interactions have been reported to be responsible for up to 3% of hospitalizations (2,3). Inappropriate events caused by drug interactions, including drug-related hospital admissions, might be prevented if patients exposed to polypharmacy are identified prospectively and monitored more closely in general practice.

It is generally considered that good prescribing is facilitated by the use of a limited number of drugs well known to the GP and sufficient to provide rational treatment for medical problems occurring in the primary healthcare system. When several prescribers are involved in the treatment of the same patient, the number of prescribed drugs may increase, and it may be difficult for the GP to keep track of all medications. This may lead to an increased risk of potential drug interactions. Tamblyn et al. thus found that about one-quarter of inappropriate drug combinations in Ireland resulted from contemporaneous prescribing by different physicians (4). In Denmark, all GPs have an agreement with the National Health Service (NHS), and the majority of the Danish population is registered with a specific practice (listed patients). However, listed patients may also receive prescriptions from doctors outside the practice. Thus, Barat et al. showed that 31% of elderly Danish patients received prescriptions from more than one prescriber, and the GP was unaware of about 25% of prescribed drugs consumed by his/her patients (5).

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Knowledge of factors responsible for exposure to potential drug interactions in primary care is limited, and studies are needed to identify groups of patients and practices at increased risk. Identification of groups of individuals at increased risk would help the GP to keep such patients under intensified monitoring and control. The aim of this study was to investigate patient- and practice-related factors associated with potential drug interactions.

Methods

Prescription data

In Denmark, drug users receive a subsidy from the NHS for most prescription drugs purchased. Reports on this subsidy are electronically transferred from pharmacies to the NHS, and, since 1990, such computerized reports have been collected in the Odense University Pharmacoepidemiologic Database (OPED) (6). The database covers the county of Funen (approx. 500 000 inhabitants) and includes a full account of the dispensed product, the date of purchase, the person identifier number, and the prescriber. Prescriptions from different practices have different prescriber codes, but within the same practice all collaborating doctors are coded by the same prescriber code, independent of which of the physicians wrote the prescription.

For each drug user, a history of drug consumption during 1 year (1999) was generated. We assumed that consumption of a drug started the same day the drug was purchased, and calculated the duration of treatment based on the assumption of a daily intake of one defined daily dose (DDD). A DDD is a technical unit, established by an expert panel of the World Health Organization (WHO) as the daily maintenance dose for the main indication of the drug (7).

Exposure to polypharmacy and potential drug interactions

Individuals exposed to polypharmacy were identified by concurrent use of two or more drugs, i.e., overlapping prescriptions (8). If the quantity of one prescription was sufficient to cover more than the period to the next prescription, the two prescriptions were defined to be overlapping. For all individuals, we analysed periods of overlapping prescriptions, and we identified all pairwise combinations of drugs. Hansten and Horn's *Drug Interactions & Updates Quarterly* (9) was used to screen the database for potential drug interactions, and all interactions found were classified according to the classification proposed by Hansten and Horn. This classification is internationally accepted and used extensively throughout the world. Drug interactions were categorized as major, moderate, or minor, depending on the severity of outcome and the quality of documentation. Drug interactions that were either well documented with the potential of being harmful or had limited documentation with the potential of serious outcome were classified as major drug interaction. Drug interactions that were less likely to cause harm or less well documented were classified as moderate drug interaction. Drug interactions, regardless of the degree of documentation, with only limited risk were classified as minor drug interaction.

Practice characteristics (number of GPs working in practice, number of patients listed, number of consultations per year, age and sex distribution among listed patients) were retrieved from the NHS, and patient characteristics (age, sex, prescriber, prescriptions) from OPED.

Analysis and statistics

The prescribing scenario in the primary healthcare system can be characterized by a hierarchical structure in which prescriptions are clustered within patients, and patients are clustered within practices. We wanted to focus on the effects of exposure to potential drug interactions at both the patient and practice levels of this hierarchy. We applied a two-level random coefficient regression model to test the relation between the risk of exposure to inappropriate drug combinations and factors related to patients and practices. The outcome variable was whether or not patients exposed to polypharmacy took drugs with potential major or moderate interactions, and a multilevel logistic regression model for binary response was used for the analysis. This model accounts for intragroup correlations due to the fact that patients listed at the same practice share some characteristics that may influence the risk of exposure to drug interactions. The model permits allocation of the variation separately to patients and practices because the random error has two additive components, one for the patient level and one for the practice level. As independent variables, we applied two blocks of variables: one block containing factors related to patients (gender, age, number of simultaneous drugs, number of different prescribers) and one block containing factors related to practice (solo/group practice, number of patients listed per GP, number of consultations per day, percentage of elderly patients [>65 years] listed, percentage of female patients listed).

All analyses were performed by means of the statistical programs STATA version 9.0 (10) and MLWin version 2.0 (11). Four models were estimated sequentially. Model 0 was the "empty"

model. This model did not include any explanatory variables, only the random effects of the clustering of patients to practices. Model 1 included patient characteristics, model 2 practice characteristics, and model 3 combined both sets of explanatory variables. In models 1–3, the coefficients were fixed, except for the intercept, which varied randomly.

Results

During 1 year, one-third of the population did not receive any prescriptions, one-third was exposed to monotherapy, and one-third to concurrent use of two or more drugs (polypharmacy) (Figure 1). The number of concurrently used drugs varied from two to 23 (average 3.4 drugs). Most (29%) individuals exposed to polypharmacy were not treated with drugs carrying a risk of interaction, but 6% of the population experienced treatment with potentially interacting drugs. The prevalence of potential drug interactions increased with age.

Figure 2 shows the risk of potential drug interactions in patients exposed to polypharmacy in relation to the number of simultaneous drugs used. A clear relation was found between the number of simultaneous drugs used and the risk of potential drug interactions. Nearly half of individuals exposed to 5–7 drugs were at risk of potential drug interactions. Moderate drug interactions were the most frequent type of drug interactions for all classes of polypharmacy. A clear relation was found between the number of prescribers and the risk of potential drug interactions in patients exposed to polypharmacy (Figure 3). For individuals with five or more prescribers, about one-third of patients exposed to polypharmacy were at risk of potential drug interactions.

Table I shows practice characteristics and the prevalence of patients exposed to polypharmacy and drug interactions in solo and group practices. Exposures to polypharmacy and drug interactions were slightly higher in solo practices compared with small (2–3 GPs) and large (≥4 GPs) group practices.

Table II shows the results of the multilevel analysis. Odds ratios (ORs) for exposure to potential drug interactions (major and moderate) in patients exposed to polypharmacy are shown in relation to explanatory factors, related to practice and patients. The empty model (model 0), which does not include any explanatory variables, shows a significant effect of the clustering of patients to practice, i.e., patients listed with the same practice were more likely to have the same risk of drug interactions compared to patients listed with different practices. The intraclass correlation (ICC) was 2.3% (1.8–2.9%). After adjusting for different patient characteristics (model 1), the ICC decreased, but it remained significant. Patient sex had no effect on the risk of exposure to potential drug interactions, but age, number of prescribers, and number of simultaneously used drugs were associated with increased risk.

At the practice level (model 2), only two explanatory variables were significant: the percentage of elderly and the percentage of female patients listed with the practice. Exposure to potential drug interactions was highest in practices with a high percentage of elderly and a low percentage of female patients listed. The type of practice (solo/group), the number of GPs working in the practice, the number of consultations per year, and the patient population size did not show a significant influence on the risk of interactions among patients listed.

Model 3 shows ORs for exposure to drug interactions after adjusting for both patient and practice characteristics. The estimates of odds ratios were robust, and only minor changes were found when shifting from one model to the next. The only exception was the estimate defined by the percentage

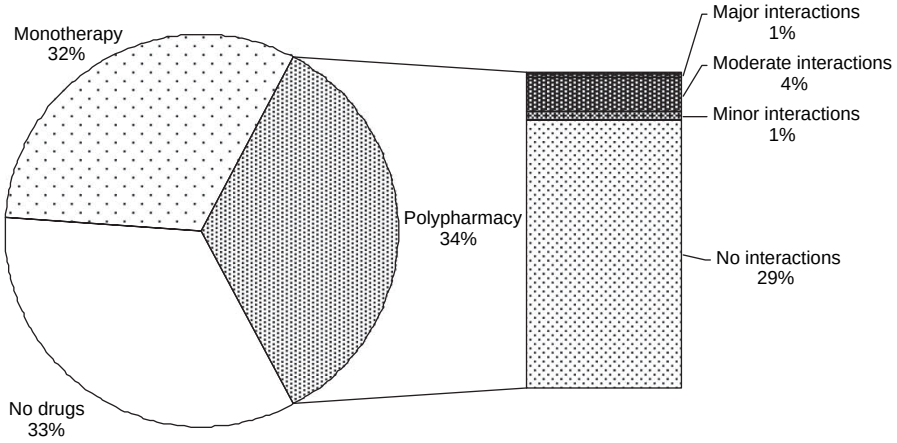

Figure 1. Distribution of patients according to drug use, polypharmacy, and potential drug interactions.

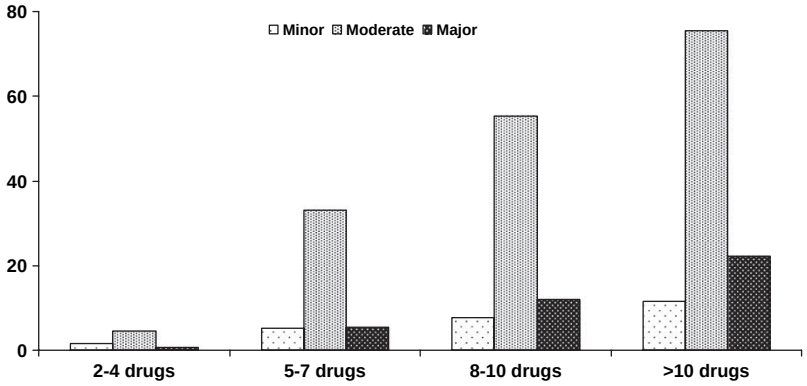

Figure 2. Percentage of individuals exposed to potential drug interactions depending on the number of simultaneous drugs used.

of elderly patients listed with the practice. In model 3, where patients' individual ages were included, the influence of the percentage of elderly patients listed was markedly reduced (compared to model 2, which only included practice characteristics), but a significant effect of practice still remained.

Discussion

Our study showed that about one-third of the population was exposed to polypharmacy (concurrent use of two or more drugs), and 6% of the population (about 15% of patients exposed to polypharmacy) was exposed to drug interactions with potentially harmful effects. A clear relation was found between the number of concurrently used drugs and the risk of interactions, and the prevalence of potential drug interactions was highest among elderly patients. The number of prescribers involved had a substantial effect on the risk of drug interactions, and for individuals with five or more prescribers about one-third of patients with polypharmacy were exposed to potential drug interactions. Patients listed with the same practice were more likely to have the same risk of drug interactions compared to patients listed with different practices, and patients listed with practices with a high percentage of elderly and a low percentage of female patients had the highest risk. However, after adjustment for factors associated with practice, patients in certain practices were still more likely to be exposed to potential interactions than patients in other practices. This could be due to measurable characteristics that were not included in our model, such as medical school of attendance, years of experience as GP, and organization of practice, and to unmeasurable characteristics related to practice tradition and practice style.

The patient population size, the type of practice (solo/group), the number of GPs working together, and the consultation rate did not influence the risk of exposure to drug interactions among patients listed.

A limitation of this study is that we only examined the exposure to potential drug interactions, not the clinical consequences. However, interpretation of clinical consequences of exposure to potential drug interactions is complicated because most agents are prescribed on the basis of indications that have their own adverse effects on patients' outcomes. Thus, the suspected interacting drug may represent an innocent bystander, unrelated to the actual outcome. Therefore, the clinical risk of exposure to drug interactions is difficult to estimate. Generally, only a minority of patients exposed to drug interactions will experience harmful effects (12). However, individuals respond differently, and potential interactions

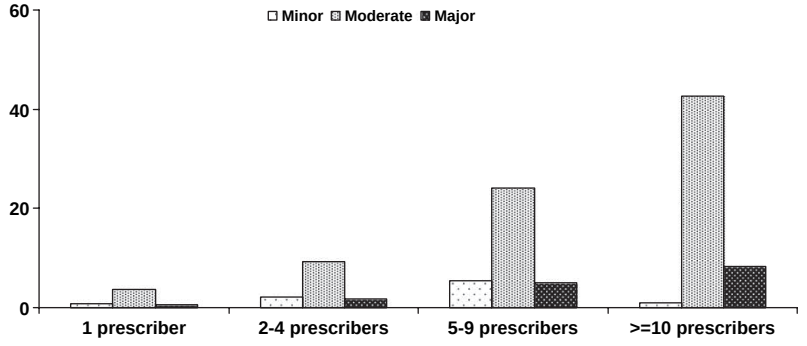

Figure 3. Percentage of individuals exposed to potential drug interactions depending on the number of prescribers (practices) involved.

Table I. Practice characteristics and prevalence of drug users exposed to polypharmacy and drug interactions in solo and group practices.

Practice type	Number of practices	Number of GPs	Number of patients	Median number of patients per GP	Median number of consultations per day	Percentage of elderly (>65 years) listed with practice	Percentage of females listed with practice	Percentage of drug users exposed to polypharmacy	Percentage of drug users exposed to minor drug interactions	Percentage of drug users exposed to moderate drug interactions	Percentage of drug users exposed to major drug interactions
Solo practices	114	114	173 995	1675	21	25.0%	50.1%	55.7%	1.4%	6.8%	1.2%
Small group practices (2–3 GPs)	58	133	206 126	1631	20	22.4%	50.7%	53.2%	1.3%	6.2%	1.1%
Large group practices (≥4 GPs)	11	50	77 986	1490	20	21.9%	51.2%	53.6%	1.5%	6.2%	1.1%
Overall	183	297	458 107	1602	20	23.4%	50.6%	54.2%	1.4%	6.4%	1.1%

denoted as major may produce no ill effects in some patients, while minor interactions may cause significant adverse effects in others. In general, drugs with a narrow therapeutic index, metabolized by cytochrome enzymes susceptible to induction or inhibition, are most likely to result in significant interactions.

Exposure to potential drug interactions was estimated from a prescription database by focusing on individuals with overlapping prescriptions, i.e., concurrent use of different drugs. The duration of treatment was calculated assuming a daily intake of one DDD. For nearly all drugs, DDD is defined as the average maintenance dose per day for the drug used on its main indication in adults. DDD is intended to be as close as possible to prescribing reality, and it is established in light of the literature, the manufacturer's advice on the data sheet, and the experience gained in the field with the drug concerned (7). DDD may, however, differ from the prescribed daily dose. Drug utilization studies show that some drugs are consumed at a lower dose than one DDD, which may result in a longer treatment period. The prevalence of overlapping treatments and potential drug interactions may therefore be higher than that found in our study. Furthermore, our data are incomplete for polypharmacy and interactions due to drugs without an established DDD (anti-neoplastic agents, dermal agents), drugs sold over the counter (salicylates, paracetamol), and non-subsidized drugs (oral contraceptives, sedatives, and hypnotics). The real number of individuals exposed to potential drug interactions is therefore likely to be higher. However, this underestimation may to some extent be counteracted by the fact that non-compliance is widespread for most drug treatments, and patients may not have taken some of the drugs prescribed.

It is a strength that we used a population-based database, covering all inhabitants in the county of Funen, corresponding to about 10% of the total Danish population. The age and sex distribution of this population is similar to the total Danish population, and the total sales of various drugs correspond to the national average (6).

In order to avoid harmful clinical consequences caused by drug interactions, it is important that the prescriber has a complete overview of all prescriptions issued to the patient. In Denmark, all GPs have an agreement with the NHS, and more than 97% of the population is registered with a GP (listed patients). The GP is responsible for the majority of all prescriptions, and "doctor shopping" is not common in Denmark. Concurrent use of potentially interacting drugs may, however, arise if the patient is referred to other doctors (specialists, outpatient

Table II. Odds ratios (OR; and confidence intervals, CI) for the association between practice/patient characteristics and exposure to potential drug interactions (major and moderate) in patients exposed to polypharmacy.

	Model 0	Model 1	Model 2	Model 3
Fixed effects				
Patient-level characteristics				
Gender (ref. women)				
Men		0.99 (0.95–1.02)		0.99 (0.93–1.03)
Age, years (ref. <30 years)				
30–49		8.65 (6.9–10.8)		8.59 (6.6–10.7)
50–69		20.06 (16.2–24.9)		19.8 (16.0–24.6)
≥70		37.98 (30.6–47.1)		37.48 (30.2–46.7)
Number of prescribers (ref. one prescriber)				
2–4 prescribers		1.06 (1.04–1.12)		1.08 (1.04–1.12)
5–9 prescribers		1.25 (1.14–1.37)		1.25 (1.15–1.38)
≥10 prescribers		2.11 (1.18–3.77)		2.11 (1.18–3.78)
Number of simultaneous drugs (ref. 2–4 drugs)				
5–7 drugs		7.14 (6.86–7.43)		7.13 (6.85–7.42)
8–10 drugs		20.68 (19.3–22.2)		20.64 (19.2–22.1)
>10 drugs		37.50 (33.74–41.68)		37.44 (33.69–41.61)
Practice-level characteristics				
Practice type (ref. single-handed practice)				
Small group practice			1.07 (0.96–1.18)	1.08 (0.98–1.22)
Large group practice			1.06 (0.78–1.44)	1.19 (0.95–1.51)
Number of patients listed			1.00 (0.99–1.00)	1.00 (0.99–1.00)
Percentage of elderly patients[a]			1.38 (1.32–1.45)	1.08 (1.02–1.14)
Percentage of female patients[a]			0.88 (0.82–0.93)	0.89 (0.83–0.95)
Random effects				
Random effects variance (intercept)				
Patient level (level 1)	1	1	1	1
Practice level (level 2)	0.078	0.035	0.024	0.028
ICC (95% CI)	2.3% (1.8–2.9)	1.1% (0.7–1.5)	0.7% (0.5–1.0)	0.8% (0.6–1.2)

[a]OR for a 10% change.
ICC: intraclass correlation between practices.

clinics, hospital departments). Our study showed that patients consulting several different doctors had a considerably increased risk of drug interactions.

We were surprised by the finding that practices characterized by a high number of female patients showed the lowest rate of potential interacting drugs. The reason for this is not clear. In general, female GPs have a higher number of female patients listed compared to male GPs. Furthermore, it has been shown that female GPs have a significantly lower prevalence of polypharmacy among their patients compared to male GPs (13). The lower risk of potential interactions may thus be a consequence of the lower risk of polypharmacy in a practice run by a female GP and dominated by female patients. We have not found other reports comparing the risk of potential drug interactions in male and female practices, and our results should be interpreted with caution until confirmed by other studies.

Many drug interactions are potentially serious, but at the same time they may be indicated treatments for patients with several chronic diseases. For example, aspirin and ACE inhibitors, if prescribed together, potentially result in an interaction that adversely affects renal function. However, most guidelines call for the concurrent use of these medications in patients with cardiovascular disease. Similarly, non-steroidal anti-inflammatory drugs (NSAIDs) may interact with medications that affect renal function (e.g., ACE inhibitors), but may be necessary in the care of elderly patients who suffer both from renal insufficiency and osteoarthritis. Exposure to potential drug interactions is therefore difficult to avoid. However, patients exposed to polypharmacy and potential drug interactions should be kept under intensified monitoring as they are at high risk of potential adverse effects caused by the treatment.

Quality-improvement programmes aimed at reducing the harmful effects of drug treatments are likely to be more effective if they focus on groups of patients at increased risk. Therefore, it is important that the GP is able to identify individuals exposed to polypharmacy and potential drug interactions. In Denmark, a nationwide population-based prescription database has cumulated all prescriptions since 1995, and prescription data for the last 2 years are now available for all prescribers through the Danish eHealth Portal (URL: www.sundhed.dk). Through this portal, all personal prescriptions (from all prescribers) can be explored after access with a digital signature. Potential interactions are clearly marked together with evidence-based information about the severity of the interaction. Future studies should be carried out to explore the effect of this programme on the exposure to potential drug interactions.

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