ORIGINAL RESEARCH ARTICLE

Drug Safety 2007; 30 (10): 911-918
0114-5916/07/0010-0911/$44.95/0

The Relationship between Number of Drugs and Potential Drug-Drug Interactions in the Elderly

A Study of Over 600 000 Elderly Patients from the Swedish Prescribed Drug Register

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Abstract

Background: Drug-drug interactions (DDIs) are of great concern, as they are known to be related to adverse drug reactions and hospitalisations. In addition, many DDIs are regarded as predictable and avoidable; therefore, they may be considered as targets for education and interventions.

Objective: To analyse the relationship between number of dispensed drugs and the probability of potential DDIs among the elderly by using the new Swedish Prescribed Drug Register.

Methods: We analysed data on age, sex and dispensed drugs for people aged ≥75 years who were registered in the Swedish Prescribed Drug Register from October to December 2005, and constructed a list of current prescriptions for every individual on the arbitrarily chosen date of 31 December 2005. Thereafter, we included those who had at least two dispensed drugs to capture the elderly population at risk of being exposed to DDIs (n = 630 743). The main outcome measures were potentially clinically relevant DDIs (type C), which may require dose adjustment, and potentially serious DDIs (type D), which should be avoided.

Results: The prevalence of type C potential DDIs was 26% and of type D potential DDIs 5% in the study population. There was a strong association between number of dispensed drugs and the probability of type C potential DDIs and an even stronger association for type D potential DDIs, after adjustment for age and sex. In addition, the probability of type D potential DDIs decreased with increasing age, and women had a lower probability of type D potential DDIs than men.

Conclusion: There seems to be a strong relationship between number of dispensed drugs and potential DDIs, especially for potentially serious DDIs, which has implications for the importance of trying to minimise the number of drugs prescribed in the elderly. Our findings that the probability of potentially serious DDIs decreases with increasing age among the elderly and that elderly women

have a lower probability of potentially serious DDIs than elderly men need to be verified and investigated by further research.

Background

Drug-drug interactions (DDIs) occur when one drug interferes with the pharmacological actions of another drug.[1] DDIs are of great concern, as they are known to be related to adverse drug reactions (ADRs) and hospitalisations.[2-10] Also, a large proportion of DDIs are regarded as predictable and avoidable,[5,8,11] and may therefore be considered as targets for education and interventions. Studies on the frequency of potential DDIs have reported rates ranging from 4% to 46%;[2,5,7,9,12-22] however, these studies vary greatly regarding assessment of DDIs, participants and setting. In Sweden, the prevalence of potential DDIs in people aged 15–95 years has been estimated to be about 14%.[20]

The focus of our DDI study is on the elderly. Older people are more frail and sensitive to ADRs and also consume more drugs than other age groups, and are thereby most exposed to potential DDIs.[23] Therefore, prescribing for the elderly requires special caution, which involves the challenge of balancing the problems related to ADRs without denying older people potentially valuable drug therapy.

To date, there is no consensus about the nature of the relationship between the number of drugs and potential DDIs. Studies have reported a general association between an increased number of drugs and potential DDIs;[12,13,16,19,24-28] however, only a few have examined the nature of this relationship.[19,25-27] Nevertheless, it has been suggested that the relationship between number of drugs and probability of potential DDIs could be exponential[29,30] or linear.[25,27] Previous research on the relationship between the number of drugs and potential DDIs has often been limited by small study samples, which is especially evident in studies on the elderly. Therefore, we wanted to investigate potential DDIs among the elderly by using the Swedish Prescribed Drug Register. This new register offers countless possibilities for studying drug use among the elderly, as well as other groups in the society.

The aim of this study was to analyse the relationship between number of dispensed drugs and the probability of potential DDIs in a large study population of people aged ≥75 years.

Methods

Study Population

The Swedish Prescribed Drug Register contains data on all dispensed prescriptions for the entire Swedish population (about 9 million inhabitants) linked though the use of unique personal identification numbers.[31] The Register does not include data on over-the-counter drugs, herbal drugs, drugs used in hospitals or from drug storerooms sometimes used in nursing homes.

We analysed data from 732 228 individuals aged ≥75 years who were registered in the Swedish Prescribed Drug Register from October to December 2005 with information about every individual's age, sex and dispensed drugs (amount of drug, date of redemption and dosage, i.e. from the prescriptions written by the prescribers).

First, information from the 3-month period about date of redemption, amount of drug and prescribed dosage was processed to calculate the duration of drug exposure.[32] When prescribed dosage was incomplete or missing, we assumed 0.9 defined daily doses (DDDs)[33] for regularly used drugs (based on calculations from prescribed doses of the amount of DDDs for regularly used drugs among the elderly in the database) and 0.5 DDDs (50% of 0.9) for drugs prescribed as needed, as indicated on the prescription. We assumed 1 DDD for drugs for external use and for the eye.

Secondly, a list of current prescriptions was constructed for every individual on the arbitrarily chosen date of 31 December 2005. If a patient was dispensed the same drug in different doses during the study period, it was counted as one dispensed drug. Finally, every individual's list of prescriptions

was analysed with regard to potential DDIs by the software programme Monitor (Quality Pharma Medtech AB, Västerås, Sweden). We only included those who had an overlap of duration of at least two dispensed drugs,[25] on the arbitrarily chosen date of 31 December 2005, to capture the elderly population at risk of being exposed to DDIs (n = 630 743).

The study was approved by the ethical board in Stockholm (Dnr 2006/948-31).

Definitions

The dispensed drugs were classified according to the anatomical therapeutic chemical (ATC) classification system, as recommended by the WHO.[33] Potential DDIs were classified according to the Swedish system developed by Sjöqvist, which is published in the Swedish *Physicians' Desk Reference*.[34] In brief, the DDIs are divided into four levels of clinical relevance: type A (probably no clinical relevance), type B (clinical relevance not yet established), type C (potentially clinically relevant) and type D (potentially serious). We focused on the two more relevant and serious types of DDIs: type C, which may require dose adjustment and type D, which should be avoided.[15,25,34]

Age was categorised into four groups: 75–79 (reference group), 80–84, 85–89 and ≥90 years. Number of dispensed drugs was divided into seven categories: 2–4 (reference), 5–7, 8–10, 11–13, 14–16, 17–19 and ≥20 drugs.

Statistical Analysis

We used logistic regression to study the association between number of dispensed drugs and potential DDIs (type C and D), with adjustment for age and sex. The results are shown as odds ratios (ORs) with 95% confidence intervals. SPSS 14.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for the analyses.

Results

The mean age among the 630 743 participants was 82 (± 5.3) years and they had on average 6.2 (± 3.7) dispensed drugs per person and 62% were women (table I). The five most frequently dispensed drugs were antithrombotic agents, β-adrenoceptor antagonists (β-blockers), high-ceiling diuretics, hypnotics/sedatives and other (non-narcotic) analgesics and antipyretics.

One or more potentially clinically relevant DDIs (type C) were present among 26% of the elderly and one or more potentially serious DDIs (type D) were present among 5%. The most common potential DDIs (type C and type D) are given in table II.

The logistic regression analyses showed that there was a strong association between number of dispensed drugs and the probability of type C potential DDIs and, especially, type D potential DDIs (tables III and IV). The probability of type D potential DDIs decreased with increasing age (table IV), although the number of dispensed drugs increased with increasing age (75–79 years: 5.6 drugs; 80–84 years: 6.1 drugs; 85–89 years: 6.7 drugs; and ≥90 years: 7.1 drugs). Women had a lower probability of type D potential DDIs than men (table IV). We also performed logistic regression analyses of type C and type D DDIs, stratified by sex to investigate effect modification; however, there were no large differences in the ORs for number of dispensed drugs between men and women, after adjustment for age.

Table I. Characteristics of the elderly study population from the Swedish Prescribed Drug Register, 2005 (n = 630 743)

Characteristics of study population	n (%)
Age (years)	
75–79	224 935 (35.7)
80–84	206 784 (32.8)
85–89	131 874 (20.9)
≥90	67 150 (10.6)
Sex	
Male	237 148 (37.6)
Female	393 595 (62.4)
Number of dispensed drugs	
2–4	251 794 (39.9)
5–7	195 932 (31.1)
8–10	106 088 (16.8)
11–13	47 590 (7.5)
14–16	18 848 (3.0)
17–19	7 036 (1.1)
≥20	3 455 (0.5)

Table II. The most common potential drug-drug interactions (DDIs) in the Swedish Prescribed Drug Register, 2005

Interactions	Rate/1000 persons
Type C (potentially clinically relevant DDIs)	
Furosemide + enalapril	51
Furosemide + digoxin	49
Furosemide + ramipril	27
Warfarin + paracetamol (acetaminophen)	12
Digoxin + spironolactone	12
Type D (potentially serious DDIs)	
Aspirin (acetylsalicylic acid) + diclofenac	9
Aspirin + naproxen	4
Aspirin + ibuprofen	4
Potassium-sparing diuretic + potassium	4
Aspirin + warfarin	4

Figure 1 shows the prevalence of type C potential DDIs as a function of number of dispensed drugs in the study population. The prevalence of type C potential DDIs increased with number of dispensed drugs; however, the increase became weaker as the number of dispensed drugs increased.

On the other hand, the relationship between the number of dispensed drugs and type D potential DDIs became stronger as the number of dispensed drugs increased, as shown in figure 2.

Discussion

Main Findings

Our results indicate that there is a strong relationship between the number of dispensed drugs and the probability of potential DDIs in the elderly, after adjustment for age and sex. Further, the relationship for potentially serious DDIs (type D) seems stronger than for potentially clinically relevant DDIs (type C). It has been suggested that the relationship between number of drugs and probability of potential DDIs would be exponential[29,30] or linear.[25,27] We cannot conclude any of these two alternatives, although the relationship between number of dispensed drugs and potentially clinically relevant DDIs seems to be of a more linear nature, whereas the relationship between number of dispensed drugs and potentially serious DDIs seems to be of a more exponential nature.

Regarding the most common DDIs, our results are in line with previous research[13,14,25,35,36] and reflect morbidity patterns in old age. According to our results, aspirin (acetylsalicylic acid) and an NSAID is the most common potentially serious DDI (type D), and type D DDIs are advised to be avoided.[34]

Moreover, our results suggest that the probability of potentially serious DDIs decreases with increasing age among the elderly, after adjustment for sex and number of dispensed drugs. The same kind of finding has been reported by others.[25] One explanation for this finding is the survivor bias of people who live past 90 years of age. However, the opposite relationship has also been found,[14,19,20] although those studies have not focused exclusively on the elderly, have used broader definitions of age groups and have not adjusted for sex and number of drugs. Also, we observed that elderly women seem to have a lower probability of potentially serious DDIs than elderly men, after adjustment for age and number of dispensed drugs. Similar findings of fewer potential DDIs among women have been seen in other studies.[20,25] Nevertheless, no sex difference has also been reported,[13,17,19] as well as the opposite scena-

Table III. Adjusted odds ratios (ORs) with 95% confidence intervals for potentially clinically relevant drug-drug interactions (type C) among elderly from the Swedish Prescribed Drug Register, 2005

Characteristics	OR (95% CI)
Age (years)	
75–79	Ref
80–84	1.04 (1.02, 1.06)
85–89	1.06 (1.05, 1.08)
≥90	0.93 (0.92, 0.96)
Sex	
Male	Ref
Female	1.00 (0.99, 1.01)
Number of dispensed drugs	
2–4	Ref
5–7	4.00 (3.93, 4.07)
8–10	8.29 (8.13, 8.44)
11–13	13.59 (13.27, 13.90)
14–16	20.47 (19.80, 21.16)
17–19	30.17 (28.57, 31.86)
≥20	45.62 (41.91, 49.66)

Ref = reference group.

Table IV. Adjusted odds ratios (ORs) with 95% confidence intervals for potentially serious drug-drug interactions (type D) among elderly from the Swedish Prescribed Drug Register, 2005

Characteristics	OR (95% CI)
Age (years)	
75–79	Ref
80–84	0.90 (0.88, 0.93)
85–89	0.83 (0.81, 0.86)
≥90	0.75 (0.72, 0.78)
Sex	
Male	Ref
Female	0.91 (0.89, 0.93)
Number of dispensed drugs	
2–4	Ref
5–7	3.76 (3.60, 3.92)
8–10	7.78 (7.45, 8.11)
11–13	12.95 (12.38, 13.55)
14–16	20.64 (19.60, 21.73)
17–19	32.12 (30.12, 34.25)
≥20	55.75 (51.59, 60.25)

Ref = reference group.

rio where women have a higher probability of DDIs than men.[27] Again, these studies have not focused solely on the elderly and have not adjusted for age and number of drugs.

Limitations

We have only used data on the elderly who were registered in the Swedish Prescribed Drug Register from October to December 2005 and who had at least two dispensed drugs according to our method, which corresponds to 79% (630 743/799 101)[37] of the population ≥75 years in Sweden. Furthermore, the Swedish Prescribed Drug Register does not include data on over-the-counter drugs, herbal drugs, drugs used in hospitals or from drug storerooms sometimes used in nursing homes, which may underestimate the drug use and, subsequently, potential DDIs.

Moreover, our method is built on an assumption that all current drugs used by an individual were dispensed during the observed 3-month period, which is based on the fact that drugs are prescribed for use during at most 90 days in Sweden. Therefore, we might miss drugs that were dispensed before the 3-month period and used slower than intended. At the same time, we run a risk of including drugs that were dispensed during the 3-month period but where the drug use was discontinued prematurely. Our method is also built on interpretations of the pre-

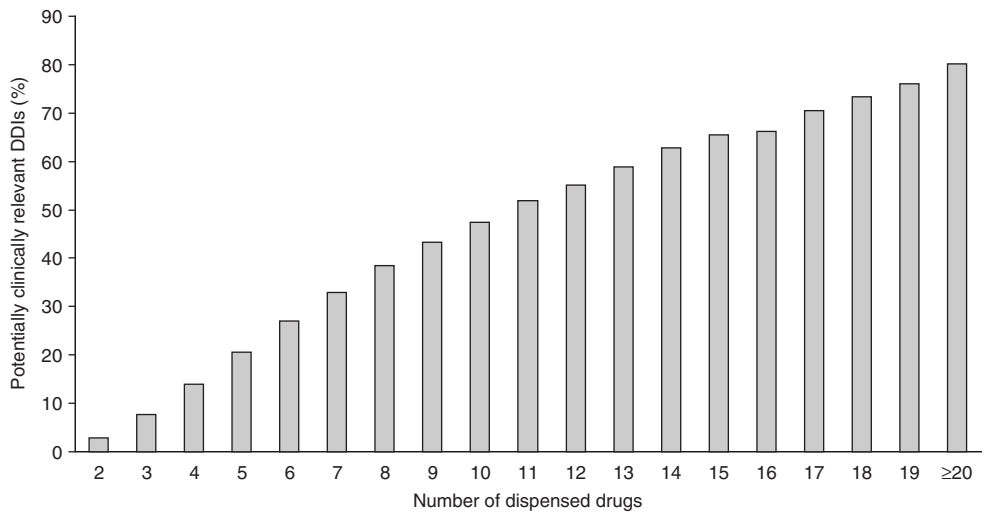

Fig. 1. Prevalence of potentially clinically relevant (type C) drug-drug interactions (DDIs) as a function of number of dispensed drugs among 630 743 people aged ≥75 years from the Swedish Prescribed Drug Register, 2005.

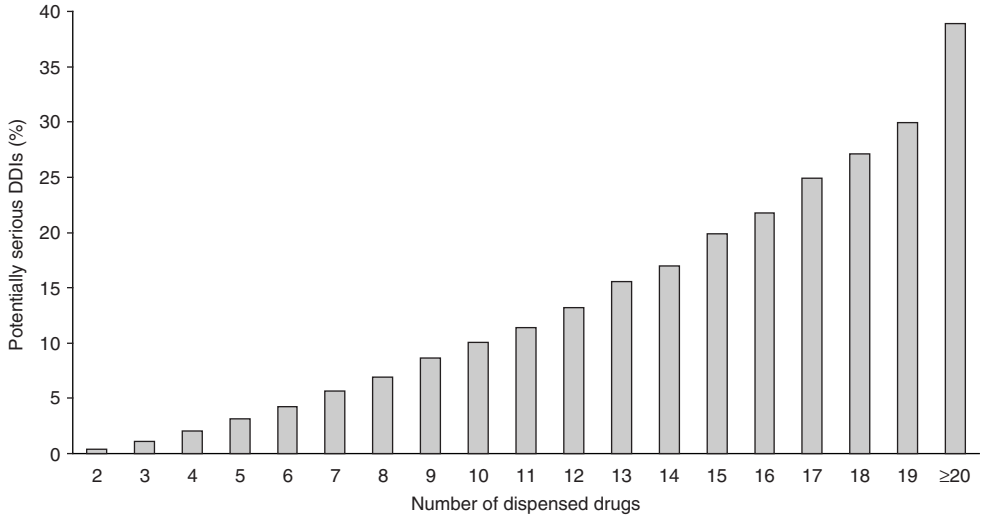

Fig. 2. Prevalence of potentially serious (type D) drug-drug interactions (DDIs) as a function of number of dispensed drugs among 630 743 people aged ≥75 years from the Swedish Prescribed Drug Register, 2005.

scribed dosages of the dispensed drugs, as well as assumptions about DDD when the information about dosage was incomplete or missing.

Furthermore, we included the variables age, sex and number of dispensed drugs in our analyses. There are other factors, e.g. co-morbidity, that may affect potential DDIs and residual confounding can not be ruled out. However, we did not have access to that kind of data in the Swedish Prescribed Drug Register.

Potential DDIs are not the same as actual DDIs.[11] Bearing this in mind, we only included potentially clinically relevant type C DDIs, which may require dose adjustment, and potentially serious type D DDIs, which should be avoided. Potentially clinically relevant DDIs (type C) can be controlled by dose adjustment; however, they are still clinically relevant and should be recognised in the prescribing procedure.

Finally, dispensed drugs are not synonymous with used drugs, as adherence to the dispensed drugs may be poor. On the other hand, data on dispensed drugs should at least be more accurate than data on prescribed drugs.

Implications

Avoidance of potential DDIs is an important issue when trying to improve the quality of drug prescribing.[20] Many hospital admissions of older patients for drug toxicity occur after use of a drug known to cause DDIs.[8] Our results from a large study population of older people suggest a strong relationship in the elderly between number of dispensed drugs and potential DDIs, and especially for potentially serious DDIs. Therefore, it is desirable to keep the number of drugs to a minimum in the elderly. Frail elderly patients with co-morbidities should be particularly carefully monitored for DDIs.[11] In the WHOs general prescribing rules for the elderly, practitioners are advised to remember that discontinuing a drug is as important as starting it.[23] Sometimes drugs are prescribed repeatedly over a number of years, even though they may not provide any clinical benefit. This can only be evaluated if the drug is withdrawn and the patient is thoroughly monitored.[11]

In addition, practitioners should be especially cautious when prescribing drugs that are often involved in potentially serious DDIs, such as aspirin and NSAIDs.

Conclusion

There seems to be a strong relationship between the number of dispensed drugs and potential DDIs, especially for potentially serious DDIs, which has implications for the importance of trying to minimise the number of drugs in the elderly.

Future research is needed for verifying and understanding our findings that the probability of potentially serious DDIs decreases with increasing age among the elderly and that elderly women have a lower probability of potentially serious DDIs than elderly men.

Acknowledgements

The authors have no conflicts of interest that are relevant to the content of this paper. This study was supported financially by the Swedish Council for Working Life and Social Research. We thank Johan Fastbom for help with the initial processing of the data material. We are also grateful to the National Board of Health and Welfare for providing us with the data.

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