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Methods for estimating the occurrence of polypharmacy by means of a prescription database

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Abstract Objective: Concurrent use of multiple drugs (polypharmacy, PP) may cause health risks such as adverse drug reactions, medication errors and poor compliance. The objective of this study, based on data from a prescription database, was to evaluate estimators of PP in the general population.

Methods: Data were retrieved from Odense Pharmacoepidemiological Database (OPED) and consisted of all prescriptions in 1994 from a 10% random sample of drug users ($n = 26977$) in the county of Funen, Denmark. For each prescription, the period of consumption was calculated by setting the duration of treatment to equal the amount of drug purchased, as measured in defined daily doses (DDD), thereby assuming a daily intake of one DDD. PP was defined as overlapping periods of consumption for different drugs. A Venn diagram was used to illustrate and compare this estimator of PP with two other indicators of multiple-drug use: the number of drugs purchased in 3 months and the mean number of drugs used in 1 year. A receiver operating curve (ROC) was used to evaluate the possibility of predicting episodes of PP from the number of drugs purchased in 3 months.

Results: The proposed estimator of PP was robust towards changes in DDD. On an average day in 1994, the prevalence of PP was 9.9% and the standard deviation (SD) between days was 0.3%. Two to four drugs (minor PP) were used by 8.7% of the population (SD, 0.2%) and five or more drugs (major PP) by 1.2% (SD, 0.1%). The number of individuals displaying PP for the first time in 1994 stabilised after approximately 6 months, resulting in an incidence of major PP of 0.2% and of minor PP of 1.2% per month. For individuals exposed

to PP, the median number of days of exposure was 61 and 10.5% were exposed for more than 350 days of the year. Purchase of five or more drugs in the first 3 months of 1994 predicted episodes of major PP in the same year with a positive predictive value of 80%.

Conclusion: Epidemiological measures of multiple drug use can be estimated from data in a prescription database. From a conceptual point of view, an estimator based on the number of simultaneously used drugs (calculated from the date of purchase and the number of DDD) is preferable, but the number of drugs purchased in a 3-month period may also be a useful estimator.

Key words Prescription database, Multiple drug use; drug utilization, computerized drug subsidy system

Introduction

Polypharmacy (PP) is the concurrent use of multiple drugs. A number of studies have demonstrated that PP may cause health risks, such as adverse drug reactions, medication errors and poor compliance [1]. Furthermore, PP may result in unnecessary drug expenses and PP has been reported to cause increased risk of hospitalisation [2]. PP may thus be a problem for both patients and society.

Previous epidemiological studies of PP have mainly been based on surveys of highly selected populations, such as patients admitted to hospital or nursing homes [3, 4]. Only a few studies have been based on data from the general population [5]. Today, however, the emergence of large computerised prescription databases allows for population-based analysis of individual drug purchase. Methods for estimating PP from such data have, however, not been evaluated in detail and definitions of PP have varied. In one study [6], multiple drug use was assumed when two or more drugs were purchased on the same day or when one drug was purchased between two purchase dates of another drug. In other

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studies, multiple drug use was estimated from the number of drugs purchased in a 3-month period [3, 7].

As estimator for PP, we suggest the number of concurrently used drugs, calculated from the date of purchase, and the quantity of each prescription as registered in a prescription database. The aim of our study was to evaluate this measure of PP and to compare it with two alternative indicators of multiple drug use.

Materials and methods

Setting

Since 1990, all prescriptions from the population of Funen, Denmark, have been collected in a research database: Odense Pharmacoepidemiological Database (OPED). OPED has been described in detail by Hallas and Hansen [8]. The database covers all prescriptions refunded by the County Health Insurance Service of Funen.

Prescriptions of refundable medicine are computerised at the pharmacies and constitute the basis for reimbursement claims from pharmacies to the county. The computerised prescription data are transferred from pharmacies to the county and are accumulated in OPED. Each record contains a unique patient-identifier, a full account of the dispensed products, the date of purchase and the identification of the prescriber.

The prescribed daily dose and the indication for prescription are not relevant to the processing of refunds and are not recorded. The database does not contain data on drugs sold without prescription (salicylates, paracetamol, ibuprofen, some ulcer drugs, antihistamines, laxatives and some antitussive remedies) nor on drugs not subsidised by the county (oral contraceptives, sedatives and hypnotics).

Data material

To reduce the volume of the data which had to be processed, the material was restricted to a 10% random sample of drug users in 1994 ($n = 26977$) (persons with a "0" as the last digit in their OPED code-number). The denominator for the calculation of prevalence and incidence of PP was 46657, i.e. 10% of the population in Funen in January 1994 [10].

Methods

PP was defined as the concurrent use of two or more drugs. The concurrent use of two to four drugs was classified as minor PP and five or more drugs as major PP.

We assumed that the consumption of a drug started the same day as the drug was purchased and calculated the duration of treatment based on an assumption of a daily intake of one defined daily dose (DDD). Thereby, the duration of a treatment was set to equal the purchased amount of a drug as measured in DDD's. Based on this calculation, the drug regime on each day of the year was calculated for all drug users. The period of analysis was from 1 January 1994 to 31 December 1994. Prescriptions purchased in 1993 were included in the analysis, if the duration of drug use covered a period in 1994. For drugs without an established DDD (dermatological, ophthalmological, otological and antineoplastic drugs), the period of drug use was set at zero. These calculations may be somewhat arbitrarily dependent on the value of DDD agreed by the Nordic Council of Medicine [9]. To test the sensitivity of the estimates towards changes in DDD, we also processed the material with the daily drug intake set at 0.5 and at 2.0 DDD.

The incidence of PP was calculated from the number of persons who displayed PP for the first time during the last 3 months of 1994, assuming that these represented incident cases.

For comparison, two other estimates of multiple drug use were calculated for each drug user: (1) the number of drugs purchased in the first 3 months of 1994 (three-month purchase); and (2) the average number of drugs used daily in 1994 (mean number).

The relationship between the proposed indicator of PP and these two alternative indices of multiple drug use was illustrated by Venn diagrams. The usefulness of the 3-month purchase for predicting episodes of major PP, as defined above, was studied in a receiver operating curve (ROC). Predictive values, sensitivity and specificity were calculated for different values ("cut off points") of the three-month purchase.

Drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification index [9]. Drugs were differentiated and counted at the fifth level of the ATC code (e.g. frusemide C03CA01).

The study was approved by the regional ethics committee and the Danish State Registry Board.

Results

Prevalence of PP

Estimates of the prevalence of drug use, based on the proposed method, showed small variations between days. On an average day in 1994, 78.1% (SD between days, 0.4%) of the population were not using any drugs, 12.0% (SD, 0.2%) used only one drug (monopharmacy) and 9.9% (SD, 0.3%) used two or more drugs simultaneously (PP). Minor PP was used by 8.7% (SD, 0.2%) and major PP by 1.2% (SD, 0.1%).

Analysis of the sensitivity of the estimates towards changes in assumed daily intake of drugs showed that the number of individuals with minor and major PP, on an average day, was 11.5% and 1.7%, respectively, if the daily intake was set at 0.5 DDD. By setting the daily intake at 2 DDD, the corresponding figures were 6.7% and 0.9%.

Incidence of PP

The number of individuals with their first episode of PP was calculated for each month of 1994. Figure 1 shows the number of individuals subject to major PP in 1994, distributed according to the month in which PP was observed for the first time. After 6 months, the number of new individuals per month stabilised at an average of 89 (range 82–94). This number may be used as an estimate of the true incidence of major PP. This corresponds to an incidence of *first time* major PP (individuals not previously exposed to major PP in 1994) of 0.2% per month. The incidence of minor PP was 1.2% per month.

Consistency and duration of PP

Analysis of the individual consistency of drug use showed that the number of drugs used per day varied markedly throughout the year. For individuals exposed to minor PP, the median length of an episode was 20 days (range 1–365 days) and for major PP, 13 days

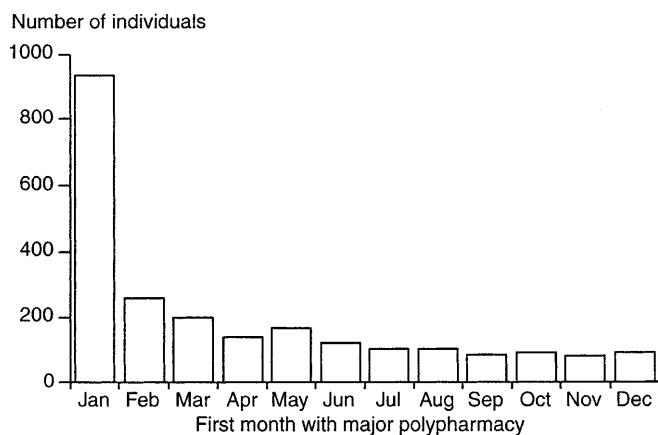


Fig. 1 Individuals subject to major polypharmacy distributed according to the month in which major polypharmacy was registered for the first time in 1994

(range 1–365 days). The median number of PP episodes per year was two (range 1–15) for all individuals subject to PP. Table 1 shows the distribution of patients exposed to PP according to the total number of days of exposure in 1994. Among individuals with minor PP, 10.5% were exposed for more than 350 days of the year and the corresponding figure for major PP was 2.6%. The median number of days of exposure per year for minor PP individuals was 61 days and for major PP individuals it was 40 days.

A total of 26977 persons was registered as drug users in 1994, corresponding to a 1-year prevalence of 57.8% (CI, 57.3–58.2%). One or more episodes of PP were observed for 13349 individuals, corresponding to a 1-year prevalence of 28.7% (CI, 28.3–29.1%). Minor PP was observed for 23.6% (CI, 23.2–24.0%) and major PP for 5.1% (CI, 4.9–5.3%).

Other indices of multiple drug use

Table 2 shows the distribution of the study population according to three different measures of multiple drug use. Approximately 5% of the population ($n = 2377$) had one or more episodes of major PP in 1994, and almost the same fractions of the population had a 3-month purchase of five or more drugs ($n = 2141$) and a mean of two or more drugs per day ($n = 2100$). The Venn diagram (Fig. 2) illustrates the similarities and differences between those three populations. Among individuals subject to an episode of major PP in 1994,

Table 2 Drug use at various percentiles (ranked according to number of drugs used) expressed by three different estimators: maximum number of drugs in simultaneous use on any day in 1994; number of drugs purchased in the first 3 months of the year; and mean number of drugs used daily in 1994

Percentile	Maximum number	3-month purchase	Mean number
75	2	1	0.3
85	2	2	0.8
90	3	3	1.1
95	5	5	2.0
99	6	8	3.4
100	18	20	7.8

71% also had a 3-month purchase of five or more drugs and 67% used a mean number of two or more drugs over the year. More than half of the individuals classified as having major PP were covered by all indices.

The ROC curve (Fig. 3) illustrates the usefulness of the 3-month purchase for predicting the occurrence of one or more episodes of major PP, as defined in the present study. More than 70% of persons subject to major PP in 1994 were identified at a cut-off level of five drugs and 99% of the population without episodes of major PP had a 3-month purchase below the cut-off point. A cut-off value of five drugs resulted in a positive predictive value of 80%.

Discussion

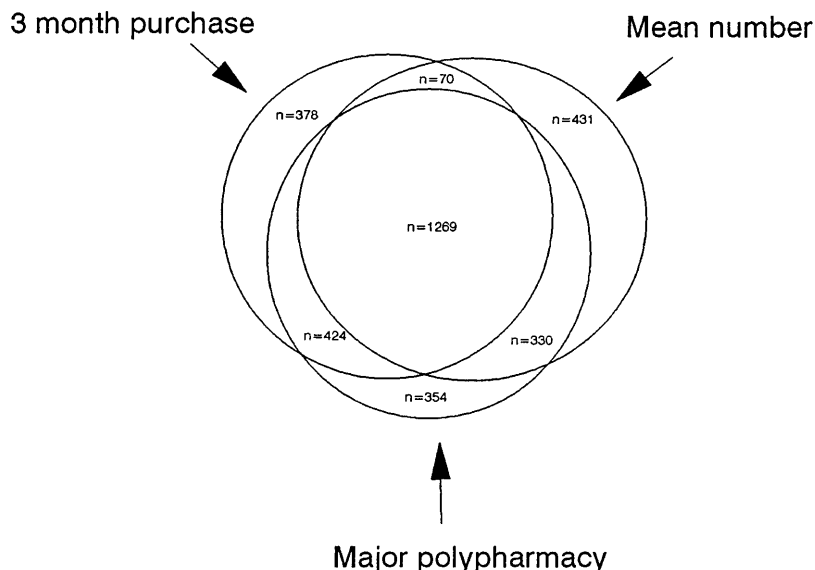
Different definitions of PP have been suggested with regard to number of simultaneously used drugs [6, 11, 12]. In the present study, major PP was defined as simultaneous treatment with five or more drugs. For most elderly people, treatment with two or three drugs does not give major medication problems, but when the number of drugs exceeds four, there is a pronounced risk of medication errors [13].

Our study estimated the prevalence of PP from the dates of drug purchase and the quantities of drugs as registered in a prescription database. The database did not contain information about the prescribed daily doses or the duration of treatment. We estimated the duration of treatment assuming a daily dose of one DDD. For nearly all drugs, a DDD is defined as the average maintenance dose per day for the drug, used for its main indication in adults [14]. However, DDD is a unit of measurement; it does not reflect the recommended or used dose for all individuals or for all diseases. Some

Table 1 Distribution of patients exposed to polypharmacy according to the number of days they were exposed in 1994

	1–10 days	11–50 days	51–200 days	201–350 days	> 350 days	Total
Minor polypharmacy (2–4 drugs)	2924 (21.9%)	3380 (25.3%)	3125 (23.4%)	2524 (18.9%)	1396 (10.5%)	13349 (100%)
Major polypharmacy (≥ 5 drugs)	556 (23.4%)	759 (31.9%)	714 (30.0%)	287 (12.1%)	61 (2.6%)	2377 (100%)

Fig. 2 Venn diagram illustrating the populations that were subject to multiple drug use, as defined by three different indices



drugs are prescribed and consumed at different dosages for different indications.

Pharmacoepidemiological studies of the population of Funen have shown that a considerable number of drugs are consumed at a lower dose than one DDD [8, 15]. PP calculated from DDD may therefore be biased. This bias, however, appears to be rather slight. If all drugs were consumed at a dose of 0.5 DDD per day, the prevalence of major PP only increased from 1.2% to 1.7% of the population.

DDDs are not established for a few drugs; they include preparations for topical use (dermatologicals, ophthal-

mologicals, otologicals) and antineoplastic drugs. Treatments with such drugs were not included in the calculations of concurrent drug use. Furthermore, our database does not contain data on drugs delivered over the counter (OTC) or on drugs not subsidised by the health insurance service. The expense of OTC drugs in Denmark has been estimated at about 20% of the total expenditure for drugs and OTC drugs are responsible for about 43% of the total number of drug packages sold [16]. An interview study showed that 27% of Danish men and 36% of women consume one or more OTC drugs within a period of 2 weeks [17]. OTC drugs are often consumed together with prescription drugs, so the actual number of individuals subject to multiple drug use is likely to be higher than the figures calculated in our study. On the other hand, not all drugs purchased by patients are used. Non-compliance is widespread for most drug treatments and it has been shown that non-compliance increases when the number of prescribed drugs increases [18, 19].

When estimating PP, all periods of treatment were mapped and the individual number of concurrently used drugs was calculated day by day, based on the number of overlapping treatments. This mapping of simultaneous drug use may be an elaborate and time-consuming method for assessing multiple drug use in large populations. As an alternative indicator, the number of drugs purchased in a 3-month period may be used. Our study showed that 80% of individuals who had purchased five or more drugs in 3 months were subject to an episode of major PP at least once during the year. Conversely, about 70% of individuals subject to concurrent use of five or more drugs in a one year period were identified by a 3-month purchase of five or more drugs. The 3-month purchase may thus be used as a rough method for identifying individuals who are subject to one or more episodes of major PP during a 1-year period.

Various estimates of the proportion of the population subject to multiple drug use have been published. In a

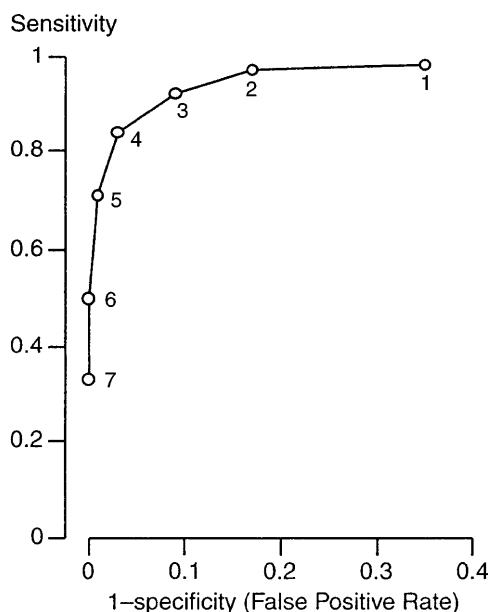


Fig. 3 Receiver operating curve illustrating the usefulness of the 3-month drug purchase for estimating major polypharmacy as defined in the present study. The figures in the curve correspond to the number of drugs purchased in 3 months

community-based study from New South Wales [20], about 20% of the elderly were currently using three or more prescription drugs. In a study of elderly people in general practice in London [21], 30% of patients were taking three or more drugs. In contrast, we found a prevalence of drug use of 22% on a random day and only 10% of the population used two or more drugs simultaneously. One of the reasons for the lower figures in our study may be the exclusion of OTC drugs, drugs without established DDD and non-subsidised drugs. Furthermore, our study was based on drug purchase in a random sample of the total population, not a selection of the elderly.

We are not aware of other attempts in the literature to estimate the incidence of PP. Our finding of an incidence of first episodes of major PP of 0.2% per month corresponds to a rate of 2–3 individuals per month per general practitioner (about 1200 listed patients per general practitioner in Denmark).

Our study shows that a prescription database can be used to estimate epidemiological measures of multiple drug use. From a conceptual point of view, an estimator based on the number of simultaneously used drugs (calculated from the date of purchase and the number of DDD) is preferable, but the number of drugs purchased during a period of 3 months may also be a useful estimator.

There is a need for further epidemiological analysis of PP in the population, including analysis of the characteristics of general practitioners who are involved in the prescription of PP.

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