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ORIGINAL ARTICLE

Multi-dose drug dispensing and inappropriate drug use: A nationwide register-based study of over 700 000 elderly

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Abstract

Objective. To investigate whether the use of multi-dose drug dispensing is associated with potentially inappropriate drug use (IDU). **Design.** Cross-sectional nationwide register-based study. **Setting.** Sweden. **Subjects.** People aged ≥ 75 years registered in the Swedish Prescribed Drug Register during October–December 2005. **Main outcome measures.** Potentially IDU, i.e. anticholinergic drugs, long-acting benzodiazepines, concurrent use of three or more psychotropic drugs, and combinations of drugs that may lead to potentially serious drug–drug interactions (DDIs). **Results.** After adjustment for age and number of dispensed drugs, any IDU, anticholinergic drugs, and three or more psychotropic drugs were associated with multi-dose drug dispensing, whereas the opposite relationship prevailed for long-acting benzodiazepines among women and potentially serious DDIs in both men and women. Among the subjects aged 75–79 years, multi-dose drug dispensing was even more strongly associated with any IDU, anticholinergic drugs, three or more psychotropic drugs in both men and women, and long-acting benzodiazepines among men. **Conclusion.** Our results indicate that multi-dose users may be more exposed to potential IDU. However, multi-dose users seem to have a lower probability of potentially serious DDIs. Future research on multi-dose drug dispensing is necessary to ensure a high quality of drug therapy within this system.

Key Words: *Drug register, elderly, family practice, inappropriate drug use, multi-dose drug dispensing, prescribing*

Multi-dose drug dispensing means that patients get their drugs machine dispensed into one unit for each dose occasion and packed in disposable bags. In each dose unit bag, all drugs intended for that dose occasion are gathered and the dose unit bags are labeled with patient data, drug contents, date and time for intake [1–4]. In Scandinavia, this service is offered as an alternative to ordinary prescription dispensing for people, mostly elderly, with regular medication use combined with difficulties in handling and administering their drugs [1–3]. Related to the multi-dose drug dispensing is unit-dose drug distribution in hospitals in which drugs that are individually packaged and labeled for specific patients are supplied from the pharmacy to the nursing units in 24-hour cycles [5–7]. This system minimizes or eliminates the preparation required for the medicine to be administered [8]. In Sweden, most multi-dose users live in nursing homes; although a growing number of community-dwelling elderly

Multi-dose is an alternative to ordinary prescription dispensing for people with regular medication use combined with difficulties in handling and administering their drugs.

- Multi-dose users may be more exposed to potentially inappropriate drug use than ordinary prescription users.
- However, multi-dose users seem to have a lower probability of potentially serious drug–drug interactions.
- Younger elderly with multi-dose drug dispensing may have the most problems with potentially inappropriate drug use.

receive this type of drug dispensing [1]. The responsible physician, most often a GP, decides whether a patient may receive multi-dose drug dispensing, and then all prescriptions are transferred to a multi-dose drug dispensing list. Thereafter,

multi-dose drug dispensing (apodos in Swedish) is performed and administered to the patient by special units within the National Corporation of Swedish Pharmacies [1]. Multi-dose drug dispensing has been suggested to reduce medication errors, increase drug adherence, and decrease waste of unused drugs [1–3,9]. The fact that the prescriber can access the complete medication list of a multi-dose patient implies that the quality of the drug therapy may improve through, for example, fewer drug–drug interactions (DDIs) and drug duplications [1]. In addition, multi-dose may facilitate routines and handling of drugs for GPs, nurses, and other health personnel [10]. However, there are also concerns that multi-dose drug dispensing may be related to increased and inappropriate drug use (IDU). Medication lists in the multi-dose drug dispensing system may be difficult to alter and reevaluation of the drug use may be done too infrequently [11].

The Swedish National Board of Health and Welfare has established quality indicators for drug use in elderly persons. These indicators are quantitative measures based on international literature on the quality of drug use in older people [12] and have recently been applied to data from elderly nursing home residents who had received multi-dose drug dispensing [4]. In our study, we focused on four of the drug-specific quality indicators, which could be applied to the Swedish Prescribed Drug Register (SPDR): anticholinergic drugs, long-acting benzodiazepines, concurrent use of three or more psychotropic drugs, and potentially serious DDIs [13]. Drugs with anticholinergic effects are important causes of urinary retention, impaired cognitive function, confusion, and delirium in older people [14–16], and should be considered inappropriate for the elderly [14,17]. Long-acting benzodiazepines have a prolonged half-life in older people, and may therefore contribute to severe sedation, cognitive impairment, and falls [17–19]. Concurrent use of three or more psychotropic drugs is a refined measure of polypharmacy, related to adverse drug reactions and drug adherence [13,20].

The aim of this study was to investigate whether the use of multi-dose drug dispensing is associated with potential IDU (i.e. anticholinergic drugs, long-acting benzodiazepines, concurrent use of three or more psychotropic drugs, and combinations of drugs that may lead to potentially serious DDIs).

Material and methods

Study population

The SPDR contains data with unique personal identification numbers of all dispensed prescriptions

in Sweden (about nine million inhabitants) [21]. We analyzed data from individuals aged 75 years and older who were registered in the SPDR during October–December 2005, with information on every individual's age, sex, and dispensed drugs (Anatomical Therapeutic Chemical [ATC] code [22], amount of prescribed drug, when the prescription was filled, and dosage [i.e. from the prescriptions written by the prescribers]). After exclusion of the 0.2% (1125/732 230) individuals with missing data on national registration of place of residence, the study population consisted of 731 105 older people (280 623 men and 450 482 women).

Information from the three-month period regarding when the prescription was filled, amount of drug, and prescribed dosage was first processed to calculate the duration of drug exposure [23]. When prescribed dosage was incomplete or missing, we assumed 0.9 Defined Daily Doses (DDD) [22] for regularly used drugs (based on calculations for regularly used drugs among the elderly in the database) and 0.45 DDDs (50% of 0.9) for drugs prescribed as needed, as indicated on the prescription. Moreover, we assumed 1 DDD for drugs for external use and for the eye. Second, based on the date of filling the prescription and the calculated duration of drug use, 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 [24].

For multi-dose users, where the prescribed dosages are missing in the SPDR, all prescriptions were regarded as current, as multi-dose drug dispensing is only for patients with regular medication use and the drugs on the multi-dose medication list are delivered every fortnight.

Definitions

In the SPDR, there is a dichotomous variable for type of drug dispensing, i.e. either ordinary prescription (used as reference category) or multi-dose.

Determination of potential IDU was based on the four quality indicators developed by the National Board of Health and Welfare: use of at least one anticholinergic drug (e.g. antihistamines, urinary antispasmodics, non-selective monoamine reuptake inhibitors, low potency neuroleptics, anticholinergic anti-Parkinsonian drugs, and anticholinergic antiemetics [4]), at least one long-acting benzodiazepine (i.e. diazepam, flunitrazepam, and nitrazepam), concurrent use of three or more psychotropic drugs (i.e. neuroleptics, anxiolytics, hypnotics/sedatives, and antidepressants), and at least one potentially

Table I. Characteristics of the 450 482 elderly women and 280 623 elderly men, Sweden, 2005.

	Women		Men	
	Multi-dose (n = 86 565)	Prescription (n = 363 917)	Multi-dose (n = 35 848)	Prescription (n = 244 775)
Mean age (years \pm SD)	86.3 \pm 5.7	81.6 \pm 5.0	84.5 \pm 5.5	80.9 \pm 4.6
Mean number of dispensed drugs (no. \pm SD)	9.4 \pm 4.4	4.7 \pm 3.3	9.3 \pm 4.3	4.5 \pm 3.2

serious DDI [4,12,13]. Any IDU was defined as being exposed to at least one of the four quality indicators [13]. Potentially serious DDIs were classified according to the Swedish system developed by Sjöqvist, which is published in the Swedish Physicians' Desk Reference [25]. In brief, the Sjöqvist system is divided into four levels of clinical relevance (types A, B, C, and D). We focused on potentially serious DDIs (type D), which should be avoided [25]. Examples of potentially serious DDIs are acetylsalicylic acid + a non-steroidal anti-inflammatory drug (NSAID), acetylsalicylic acid + warfarin, and potassium-sparing diuretics + potassium [24,26].

Age was used as a continuous variable in the regression analyses and categorized into 75–79, 80–84, 85–89, and \geq 90 years in the descriptive analyses.

Number of dispensed drugs, used as an overall measure of comorbidity [27,28], was coded as a continuous variable.

Statistical analysis

Logistic regression analysis stratified by sex was used to study the association between multi-dose drug dispensing and IDU, after adjustment for age and number of dispensed drugs. The results are shown as odds ratios (ORs) with 95% confidence intervals (CIs). SPSS 14.0 for Windows (SPSS Inc., 1989–2005) was used for the analyses.

Ethics

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

Results

About 19% of the women and 13% of the men in the study population used multi-dose drug dispensing. On average, the multi-dose users were older and used more drugs compared with the ordinary prescription users (Table I).

The descriptive analysis of IDU in Table II shows that the multi-dose users had higher prevalence of all indicators of potential IDU than prescription users. The younger elderly (aged 75–79 years) who used multi-dose drug dispensing had the highest frequency of all indicators of potential IDU. Further, most indicators of IDU were more common in women than men.

After adjustment for age and number of dispensed drugs, any IDU, anticholinergic drugs, and three or more psychotropic drugs were associated with multi-dose drug dispensing, whereas the opposite relationship prevailed for long-acting benzodiazepines among women and potentially serious DDIs in both men and women (Table III). In particular the quality indicator concurrent use of three or more psychotropic drugs was associated with multi-dose drug dispensing ($OR_{\text{women}} = 3.96$,

Table II. Potentially inappropriate drug use among 450 482 elderly women and 280 623 elderly men, Sweden, 2005.

	Any inappropriate drug use (%)	Anticholinergic drugs (%)	Long-acting benzodiazepines (%)	\geq 3 psychotropic drugs (%)	Potentially serious drug–drug interactions (%)
Multi-dose (n = 122 413)	40.3	15.3	8.8	22.1	8.8
Women	41.0	15.1	9.2	23.1	8.9
Men	38.5	15.6	7.8	19.8	8.8
75–79 years	45.9	19.2	9.8	26.7	10.1
80–84 years	41.4	15.6	8.3	23.7	9.4
85–89 years	38.9	14.2	8.0	21.2	8.8
\geq 90 years	37.4	13.8	9.5	18.9	7.6
Prescription (n = 608 692)	13.6	4.9	4.7	2.4	3.7
Women	15.0	5.5	5.5	2.9	3.6
Men	11.5	4.1	3.4	1.7	3.8
75–79 years	12.6	5.0	3.7	2.3	3.7
80–84 years	13.7	4.9	4.6	2.4	3.7
85–89 years	15.0	4.9	5.9	2.7	3.6
\geq 90 years	15.7	4.4	7.8	2.6	3.0

Table III. Adjusted¹ odds ratios (ORs) with 95% confidence intervals (95% CIs) for potentially inappropriate drug use among 450 482 elderly women and 280 623 elderly men, Sweden, 2005.

	Any inappropriate drug use	Anticholinergic drugs	Long-acting benzodiazepines	Three or more psychotropic drugs	Potentially serious drug–drug interactions
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Women					
Prescription	Ref	Ref	Ref	Ref	Ref
Multi-dose	1.43 (1.40–1.46)	1.51 (1.47–1.56)	0.69 (0.66–0.71)	3.96 (3.85–4.09)	0.80 (0.77–0.83)
Men					
Prescription	Ref	Ref	Ref	Ref	Ref
Multi-dose	1.72 (1.67–1.78)	2.05 (1.97–2.14)	0.94 (0.89–1.00)	4.93 (4.70–5.17)	0.70 (0.66–0.74)

Note: ¹Adjusted for age and number of dispensed drugs.

95% CI 3.85–4.09) and $OR_{men} = 4.93$, 95% CI 4.70–5.17). After observing in the descriptive analysis that younger elderly multi-dose users had the highest frequency of IDU, we performed a subgroup analysis of this age group, stratified by sex (Table IV). This analysis revealed that multi-dose drug dispensing among 75- to 79-year-olds was even more strongly associated with any IDU, anticholinergic drugs, three or more psychotropic drugs in both men and women, and long-acting benzodiazepines among men. Potentially serious DDIs were, however, also negatively associated with multi-dose drug dispensing in this subgroup analysis.

Discussion

Principal findings

Our results indicate that multi-dose users may be more exposed to potential IDU. This may partly be explained by the higher drug use in the multi-dose than the ordinary prescription users. Nevertheless, multi-dose drug dispensing was clearly associated with any IDU, anticholinergic drugs, and concurrent use of three or more psychotropic drugs, after

adjustment for age and number of drugs. As has been suggested, the multi-dose drug dispensing lists may be regarded as complicated to make changes to and there is a risk of uncritical renewal of prescriptions [11].

In contrast, multi-dose users had a lower probability of potentially serious DDIs. The prescribing physician, most often a GP, may more easily discover DDIs when he or she has access to the complete overview of the patient's drug use [1]. This finding encourages the implementation of individual medication lists available to prescribers.

We also observed that the younger elderly with multi-dose drug dispensing had the most problems with potential IDU. However, in this age group too, potentially serious DDIs were negatively associated with multi-dose drug dispensing. Recently, a study on elderly nursing home residents who received multi-dose drug dispensing also showed that the quality of drug therapy was higher among older than younger elderly patients [4]. One explanation could be a healthy survivor effect of people who reach very old ages [4]. Notwithstanding, extra careful monitoring of younger elderly multi-dose users' medication lists may be valid.

Table IV. Adjusted¹ odds ratios (ORs) with 95% confidence intervals (95% CIs) for potentially inappropriate drug use among 155 657 women and 116 419 men aged 75–79 years, Sweden, 2005.

	Any inappropriate drug use	Anticholinergic drugs	Long-acting benzodiazepines	Three or more psychotropic drugs	Potentially serious drug–drug interactions
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Women					
Prescription	Ref	Ref	Ref	Ref	Ref
Multi-dose	1.88 (1.80–1.97)	1.64 (1.55–1.75)	0.98 (0.91–1.06)	4.63 (4.36–4.92)	0.70 (0.64–0.76)
Men					
Prescription	Ref	Ref	Ref	Ref	Ref
Multi-dose	2.05 (1.94–2.18)	2.28 (2.11–2.46)	1.36 (1.23–1.51)	5.74 (5.29–6.24)	0.56 (0.51–0.62)

Note: ¹Adjusted for age and number of dispensed drugs.

Limitations

The cross-sectional design of our study makes it impossible to draw conclusions regarding causality.

We have used data on elderly registered in the SPDR during October–December 2005, corresponding to 91% of the population 75 years and older in Sweden [29]. Further, the SPDR does not include data on over-the-counter drugs, herbal drugs, and drugs used in hospitals. Also, the register is incomplete with regard to drugs used in nursing homes, which may lead to an underestimation of drug use.

Moreover, our method for calculation of the duration of drug exposure for ordinary prescription users is built on an assumption that all current drugs were dispensed during the observed three-month period, which is based on the fact that drugs are prescribed for use for at most 90 days in Sweden. Hereby, we might miss drugs that were dispensed before the three-month period and used at a slower rate than intended. At the same time, we might include drugs that were dispensed during the three-month period but discontinued prematurely. In addition, our method is built on interpretations of the dispensed drugs' dosages in free text, as well as assumptions about DDDs when the information on dosage was incomplete or missing [13,23].

There are also possible confounding factors, e.g. comorbidity and accommodation, which are not included in the SPDR. However, we used number of dispensed drugs as an overall measure of comorbidity, as previously suggested [27,28].

Individual IDU is not the same as actual IDU. For the individual patient, a drug judged to be inappropriate by definition may sometimes be justified [12,13].

Finally, a general limitation of studies on drug registers is that dispensed drugs may not reflect what is actually used by the patients, as the adherence rate may be low.

Implications

As far as we know, the relation between multi-dose drug dispensing and IDU has not been studied before, and our findings may be useful for societies on the verge of implementing this system.

Multi-dose drug dispensing is convenient for the patients, GPs, nurses, and other health personnel [10], and may decrease the probability of potentially serious DDIs. However, there may be concerns about other types of potential IDU, perhaps due to a risk of uncritical renewal of prescriptions and less inclination to make changes to medication lists in the multi-dose drug dispensing system.

Moreover, the divergent patterns for the four measures of IDU in our study highlight the need for studying different aspects of IDU, and not only one summarized measure [13].

Future research

Future research on multi-dose drug dispensing is necessary for ensuring a high quality of drug therapy within this system. In addition, more elaborate analyses of younger elderly multi-dose users' problems with potential IDU are desirable.

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