Measuring psychotropic drug exposures in register-based studies – validity of a dosage assumption of one unit per day in older Finns

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Key words

psychotropic drugs, exposure, dose, older people, defined daily dose

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Received 29 March 2011;
revised 28 October 2011;
accepted 17 January 2012

Abstract

Pharmacoepidemiological studies provide valuable information on the relationships between psychotropic drug use and adverse outcomes in older people. To minimize the influence of misclassification bias in pharmacoepidemiological studies, more emphasis should be given to methodological aspects of exposure assessment. This study evaluated the validity of a dosage assumption of one unit per day for measuring legend duration of psychotropic drug exposures among older people. Using data from the Finnish Prescription Register, the study analysed 62,320 psychotropic drug prescriptions dispensed for people aged ≥ 75 years ($n = 52,729$) in September 2009. The proportions of prescriptions in which the prescribed dose deviated from one unit per day were assessed for categories and subcategories of psychotropic drugs. The prescription was considered misclassified (a) if the prescribed drug was intended for “as needed” use, (b) if the prescription included a dose range, or (c) if the prescribed dose was below or above one unit per day. Among antidepressants, less than every fourth (23.7%) prescription was misclassified. The proportions of misclassification varied substantially across subcategories, being 13.1% for selective serotonin reuptake inhibitors (SSRIs), 25.3% for other antidepressants and 53.8% for tricyclic antidepressants. Of the benzodiazepine and antipsychotic prescriptions, 79.9% and 57.6%, respectively, were misclassified. In conclusion, the dosage assumption of one unit per day is valid for measuring the legend duration of SSRI and other antidepressant exposures among older people. Among other psychotropic drugs, the dosage assumption is likely to lead to severe exposure misclassification. Copyright © 2013 John Wiley & Sons, Ltd.

Introduction

Psychotropic drugs are frequently used by older people (Aparasu *et al.*, 2003; Johnell and Fastbom, 2009) despite their potential to cause many undesirable outcomes (Glass *et al.*, 2005; Gill *et al.*, 2007; Trifirò *et al.*, 2007; Woolcott *et al.*, 2009). In Finland, more than one-third of community-dwelling persons aged ≥ 75 years use at least one psychotropic drug (Linjakumpu *et al.*, 2002; Rikala *et al.*, 2011). Pharmacoepidemiological studies provide valuable information on the relationships between psychotropic drug use and adverse outcomes, particularly among older people who are typically underrepresented in clinical trials (Giron *et al.*, 2005; Van Spall *et al.*, 2007). A valid data source is of great importance in pharmacoepidemiological studies as misclassification of a patient's exposure status lead to biased measures of association (West *et al.*, 2006). To minimize the influence of bias due to exposure misclassification, additional emphasis should be given to methodological aspects of exposure assessment.

In register-based pharmacoepidemiological studies, exposure to psychotropic drugs is usually identified using either the fixed-time window method (Liu *et al.*, 1998; Bolton *et al.*, 2008), an intention-to-treat approach (Kales *et al.*, 2007) or the legend duration method (Wang *et al.*, 2001; Gill *et al.*, 2007; Knol *et al.*, 2008; Zint *et al.*, 2010). In the fixed-time window method, used in case control designs, subjects are defined as exposed if they have been dispensed a prescription within a specific period of time before the day of the outcome event (Lau *et al.*, 1997). In an intention-to-treat approach, used in cohort designs, subjects remain on their initial exposure status until the end of follow-up (Kiri and MacKenzie, 2009). In the legend duration method, used both in case control designs and cohort designs, subjects are defined as exposed based on the theoretical duration of each prescription, the calculation of which requires information on the number of days' supply or the prescribed daily dose (Lau *et al.*, 1997). The legend duration method has advantages over the fixed-time window method and an intention-to-treat approach as it estimates actual periods of drug exposure.

However, a major limitation in the legend duration method is the fact that many prescription registers, including those of the Nordic countries, do not record information on the days' supply or prescribed daily dose in a structured format (Furu *et al.*, 2010). Therefore, several studies have calculated the legend duration of drug exposure using the defined daily dose (DDD) as a proxy for the prescribed dose (Bak *et al.*, 2002; Tiihonen *et al.*, 2009; Modén *et al.*, 2010). The DDD is defined as an assumed average maintenance dose per day for a drug

when used for its main indication in adults (World Health Organization [WHO] Collaborating Centre for Drug Statistics Methodology, 2010). However, using the DDD as a proxy for the prescribed dose may lead to exposure misclassification, since the prescribed dose of an individual patient may differ from the DDD. Among older people, in particular, antipsychotics and benzodiazepines are frequently prescribed with lower doses than those of DDDs (Hosia-Randell and Pitkälä, 2005; Cheng *et al.*, 2008). This may relate to the fact that older people are, in general, advised to be treated with lower doses of psychotropic drugs than those recommended for younger adults (Alexopoulos *et al.*, 2004; American Psychiatric Association, 2007a; Finnish Medical Society Duodecim, 2008). In addition, older people tend to suffer from indications that are treated with relatively low doses. For instance, the doses of antipsychotics recommended for behavioural and psychological symptoms of dementia are considerably lower than the DDDs for these drugs (Alexopoulos *et al.*, 2004; American Psychiatric Association, 2007b).

To avoid problems related to the DDDs, some studies have calculated the legend duration of drug exposure based on other dosage assumptions, such as one unit (e.g. tablet or capsule) per day (Gulmez *et al.*, 2009; Dall *et al.*, 2010; Helin-Salmivaara *et al.*, 2010). Making such an assumption about the daily dose is attractive because it is universally available and easy to use. However, no study has evaluated the extent of misclassification in psychotropic drug exposure assessment resulting from the dosage assumption of one unit per day among older people. Neither is there information as to whether the degree of misclassification differs between patient groups. The degree of misclassifications may vary, for instance, by indication, gender and age, because the prescribed dose is largely based on the condition being treated and the individual characteristics of a patient (WHO, 2003). In addition, the degree of misclassifications may be higher for new users than for prevalent users, since psychotropic drugs are advised to be initiated at low doses in older people (Alexopoulos *et al.*, 2001; American Psychiatric Association, 2007a, 2007b, 2009).

Using data from the Finnish Prescription Register, this study aimed to evaluate the validity of a dosage assumption of one unit per day for measuring legend duration of psychotropic drug exposures among people aged ≥ 75 years. Furthermore, the study assessed whether the validity of this dosage assumption is influenced by patient characteristics. Finally, the study estimated the potential advantages of the dosage assumption of one unit per day over the dosage assumption of DDD per day.

Methods

The Finnish Prescription Register

The Finnish Prescription Register is a nationwide pharmacy claims database maintained by the Social Insurance Institution (SII) of Finland since 1994 (Furu *et al.*, 2010). The National Health Insurance Scheme provides drug reimbursement for all 5.3 million residents of Finland, except for people staying in public nursing homes or hospitals, where the drugs are supplied by the provider of the services. The reimbursement system involves three refund categories that are graded according to medical criteria based on the severity of the illness and the necessity of the drug treatment (Finnish Medicines Agency and Social Insurance Institution, 2010). In all categories, drugs are reimbursed for a maximum period of three months in one transaction (e.g. a package of 100 units with a daily dose of one unit).

The Finnish Prescription Register includes information on reimbursed drug purchases dispensed in Finnish community pharmacies (Furu *et al.*, 2010). The Prescription Register does not contain information on non-reimbursable drugs (including most of the over-the-counter drugs, drugs awaiting eligibility for reimbursement and drugs that cost more than a reasonable wholesale price); therefore, for example, some small packages and lower strengths of benzodiazepines and tricyclic antidepressants are not covered. Neither is there information on prescribed doses in a structured format. However, dosing instructions are

recorded as a free text (e.g. ½–1 tablets in the evening for insomnia, not for regular use) and saved for a period of 1.5 years from the dispensing date. This information is not typically used in register-based studies because the manual conversion into numerical form is time-consuming and oftentimes not even possible in retrospective studies.

Data collection

The study population consisted of people aged ≥ 75 years (born 1934 or before) with at least one purchase of psychotropic drugs identified in the Prescription Register in September 2009. Psychotropic drugs were defined as antipsychotics (N05A), benzodiazepines (N05B and N05C excluding buspirone, hydroxyzine, valerian and melatonin) and antidepressants (N06A, N06CA01) according to the Anatomical Therapeutic Chemical (ATC) classification recommended by the WHO (WHO Collaborating Centre for Drug Statistics Methodology, 2010) (Table 1). For each subject in the study population, all purchases of psychotropic drugs in September 2009 were extracted. However, if a subject had purchased the same drug (fifth ATC-level) more than once in September, only the first purchase was included.

The following information was extracted for each subject: gender, age (at the end of 2009) and history of psychotropic drug use (ATC codes) over a six-month period prior to September 2009 (1 March and 31 August 2009). Information extracted for each purchase of a psychotropic drug in September 2009 included ATC code,

Table 1 The categories and subcategories of psychotropic drugs

<i>Antipsychotics</i>	<i>ATC-code N05A</i>
Typical	chlorpromazine, levomepromazine, perphenazine, periciazine, thioridazine, haloperidol, melperone, flupentixol, chlorprothixene, zuclopenthixol, pimozide, sulpiride, sertindole, ziprasidone, clozapine, olanzapine, quetiapine, risperidone, aripiprazole
Atypical	
Lithium	lithium
<i>Benzodiazepines</i>	<i>ATC-codes N05B, N05C (excluding buspirone, hydroxyzine, valerian and melatonin)</i>
Long-acting	diazepam, chlordiazepoxide, clobazam, alprazolam, nitrazepam
Medium-acting	oxazepam, lorazepam, temazepam
BZD-related drugs	zopiclone, zolpidem
<i>Antidepressants</i>	<i>ATC-codes N06A, N06CA01</i>
Tricyclics	clomipramine, trimipramine, amitriptyline, nortriptyline, doxepin, amitriptyline combinations
SSRIs	fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram
MAOIs	moclobemide
Others	mianserin, trazodone, mirtazapine, venlafaxine, milnacipran, reboxetine, duloxetine

Note: Table 1 includes psychotropic drugs that were purchased by people aged ≥ 75 years in September 2009. The Prescription Register does not include information on non-reimbursable drugs (prochlorperazine, triazolam, midazolam, and zaleplon were on the market in 2009, but were non-reimbursable). BZD, benzodiazepine; SSRIs, selective serotonin reuptake inhibitors; MAOIs, monoamine oxidase inhibitors.

dosage form, strength, the quantity dispensed, dispensing date and dosing instruction (as a free text).

Data processing and analyses

The study included psychotropic prescriptions involving tablets or capsules. Information from free-text dosing instructions was manually converted into a numerical form. The recorded information included indication, prescribed number of units per day (tablets or capsules), prescribed dose per day in milligrams (calculated by multiplying the drug strength by the number of units per day), whether a prescribed dose was fixed (e.g. one tablet every evening) or range (e.g. 1–2 tablets every evening) and whether a drug was intended for “as needed” use. The drug was considered to be intended for “as needed” use if the dosing instruction included the phrase for “as needed use”, “for sporadic use”, “not for regular use”, or “not over 1–3 times per week”. Other drugs were considered to be intended for daily use.

The validity of the dosage assumption was evaluated by analysing the proportions of prescriptions for which the prescribed dose deviated from a daily dose of one unit. The prescription was considered misclassified (a) if the prescribed drug was intended for “as needed” use, (b) if the prescription included a dose range (e.g. 1–2 tablets every evening), or (c) if the prescribed dose was below or above one unit per day. If the prescription included a dose range, the minimum dose was primarily considered because older people tend to use central nervous system drugs with lower doses and less frequently than prescribed (Barat *et al.*, 2001). The proportion and type of misclassification was analysed separately for categories and subcategories of psychotropic drugs (Table 1).

To assess the influence of patient characteristics on the validity of the dosage assumption, the proportions of misclassification were analysed by gender and age groups. In addition, the proportions of misclassification were analysed separately for different indications as identified in free-text dosing instructions. Furthermore, the proportions of misclassification were analysed for subjects who purchased ≤ 30 or > 30 units. A smaller quantity purchased was considered to be indicative for either a dose below one unit per day or an irregular pattern of use, because with a regular dose of one unit per day drugs are usually purchased for a three-month period (a package of 100 units). Moreover, the proportions of misclassification were analysed for new and prevalent users. Subjects were defined as new users if they had not purchased a drug belonging to the same therapeutic category during the six-month period before September 2009. For instance, users of citalopram were considered new users if they had not purchased any

antidepressant between 1 March and 31 August 2009. Statistically significant differences between the patient characteristics were analysed using Pearson χ^2 test.

The potential advantages of the dosage assumption of one unit per day over the dosage assumption of DDD per day were estimated for the most frequently prescribed individual drugs (≥ 100 prescriptions). The percentages of prescriptions including a dose below or above one unit per day were compared with the percentages of prescriptions including a dose below or above the DDD per day. In addition, the DDDs were compared with the most frequently prescribed doses in milligrams (MCPD).

Permissions

The study protocol was approved by the SII. According to Finnish law, ethics committee approval was not required because the study used only register data and the subjects were unidentifiable.

Results

Psychotropic drug prescriptions

A total of 52,729 subjects aged ≥ 75 years purchased psychotropic drugs in September 2009. The majority of them were women (72.1%, $n = 38,019$) and the mean age was 82.2 years (range 75–106). Overall, the data comprised 62,794 psychotropic prescriptions, of which 99.5% ($n = 62,474$) involved tablets or capsules. After excluding 154 prescriptions with no dosing instruction available, the final data consisted of 62,320 prescriptions. The majority of the prescriptions were for benzodiazepines (56.9%, $n = 35,455$), followed by antidepressants (29.9%, $n = 18,607$) and antipsychotics (13.3%, $n = 8258$).

Overall proportion of misclassified prescriptions

Assuming a daily dose of one unit, the overall proportion of misclassified prescriptions was highest for benzodiazepines (79.9%) and antipsychotics (57.6%), with minor variation between subcategories (Table 2). Among antidepressants, less than every fourth (23.7%) prescription was misclassified. The proportions of misclassification showed considerable variation across subcategories of antidepressants, being lowest for selective serotonin reuptake inhibitors (SSRIs) (13.1%) and other antidepressants (25.3%) and highest for tricyclic antidepressants (53.8%) and monoamine oxidase inhibitors (MAOIs) (74.2%)

Table 2 The proportions of misclassification when assuming a daily dose of one unit

	<i>n</i>	As needed % (<i>n</i>)	Dose range % (<i>n</i>)	One unit per day ¹		Overall misclassification % (<i>n</i>) ²
				Below % (<i>n</i>)	Above % (<i>n</i>)	
<i>Antipsychotics</i>	8258	1.8 (145)	12.4 (1020)	13.6 (1126)	36.9 (3046)	57.6 (4753)
Typical	1516	3.8 (57)	17.0 (258)	7.3 (111)	42.3 (641)	60.6 (919)
Atypical	6665	1.3 (88)	11.4 (760)	15.2 (1012)	35.3 (2353)	56.7 (3777)
Lithium	77	0 (0)	2.6 (2)	3.9 (3)	67.5 (52)	74.0 (57)
<i>Benzodiazepines</i>	35455	52.9 (18763)	49.8 (17647)	39.5 (14009)	8.6 (3064)	79.9 (28322)
Long-acting	3157	50.7 (1601)	54.0 (1706)	21.2 (669)	20.5 (648)	85.6 (2703)
Medium-acting	13332	46.7 (6232)	49.7 (6628)	31.3 (4178)	14.2 (1896)	78.2 (10425)
BZD-related drugs	18966	57.6 (10930)	49.1 (9313)	48.3 (9162)	2.7 (520)	80.1 (15194)
<i>Antidepressants</i>	18607	0.9 (175)	9.8 (1823)	9.6 (1783)	8.6 (1600)	23.7 (4412)
Tricyclics	2499	4.2 (106)	29.9 (746)	4.6 (114)	24.6 (615)	53.8 (1344)
SSRIs	8514	0.02 (2)	3.9 (330)	6.0 (513)	5.3 (447)	13.1 (1113)
MAOIs	62	0 (0)	0 (0)	6.5 (4)	67.7 (42)	74.2 (46)
Others	7532	0.9 (67)	9.9 (747)	15.3 (1152)	6.6 (496)	25.3 (1909)

¹If the prescription included a dose range, the minimum dose was considered.

²The prescription was considered misclassified (a) if the prescribed drug was intended for “as needed” use, (b) if the prescription included a dose range or (c) if the prescribed dose was below or above one unit per day.

Note: BZD, benzodiazepine; SSRIs, selective serotonin reuptake inhibitors; MAOIs, monoamine oxidase inhibitors.

Types of misclassification

Prescriptions intended for “as needed” use were mainly for benzodiazepines (Table 2). Specifically, over half of the benzodiazepine prescriptions (52.9%), but only few of the antipsychotic (1.8%) and antidepressant prescriptions (0.9%) were for “as needed” use. Prescriptions including a dose range were most common among benzodiazepine prescriptions (49.8%). Of the antipsychotic and antidepressant prescriptions, every tenth (12.4% and 9.8% respectively) included a dose range. The majority of the antipsychotic,

benzodiazepine and antidepressant prescriptions including a dose range had a dose one unit per day within the minimum and maximum dose (84.8%, 96.1% and 91.1%, respectively).

The prescribed numbers of units per day are shown in Figure 1 for antipsychotic, benzodiazepine and antidepressant prescriptions. Considering the minimum of the dose range, the prescribed dose was below one unit in 13.6% of the antipsychotic prescriptions and above one unit in 36.9% of the antipsychotic prescriptions (Table 2). Among benzodiazepines, the prescribed dose was below one unit

Figure 1 Number of units per day for antipsychotic (*n* = 8,258), benzodiazepine (*n* = 35,455) and antidepressant (*n* = 18,607) prescriptions.

in 39.5% of the prescriptions and above one unit in 8.6% of the prescriptions. Among antidepressant prescriptions, the prescribed dose was nearly as often below one unit (9.6%) as above one unit (8.6%). Considering the maximum of the dose range, the prescribed dose was above one unit in 43.9% of the antipsychotic prescriptions, 25.3% of the benzodiazepine prescriptions and 13.9% of the antidepressant prescriptions.

Misclassification by patient characteristics

Since the overall proportion of misclassified prescriptions was high among antipsychotics and benzodiazepines, the influence of patient characteristics was analysed only for antidepressant prescriptions. Among tricyclic antidepressants, about half of the prescriptions were misclassified regardless of patient characteristics (Figure 2). Among other antidepressants, the proportion of misclassifications varied substantially by indication (13.8–50.4%) and was higher for new users (36.4%) than for prevalent users (24.1%). Among new users, the majority of the misclassified prescriptions included a dose below one unit (29.4%). In addition, the proportion of misclassifications was higher for those who purchased ≤ 30 units than for those who purchased > 30 units both among other antidepressants (31.4% versus 22.1%) and SSRIs (23.3% versus 11.6%). The difference between those who purchased ≤ 30 and > 30 units emerged both among new users (38.5% versus 32.1%, p -value < 0.001) and prevalent users (29.6% versus 21.6%, p -value < 0.001) of other antidepressants and among prevalent users of SSRIs (25.7% versus 11.3%, p -value < 0.001). Among new users of SSRIs, the difference was small (17.8% versus 15.0%, p -value = 0.248).

Comparison between dosage assumption and DDD

Considering the minimum of the dose range, the percentages of prescriptions with a daily dose of one unit were substantially higher than the percentages of prescriptions with a daily dose of the DDD (Table 3). Prescriptions for nirtazepam, zopiclone, zolpidem and paroxetine were an exception; among them the percentages were similar. In almost all prescriptions for antipsychotics, tricyclic antidepressants and oxazepam, the prescribed dose was below the DDD. Compared with the DDDs, the MCPDs were lower for the majority of the psychotropic drugs. The DDDs and the MCPDs were in agreement for nirtazepam, temazepam, zopiclone, SSRIs and duloxetine. If the maximum of the dose range was considered, the DDDs and the MCPDs were in agreement for zolpidem as well.

Discussion

The findings of this study indicate that the dosage assumption of one unit per day is valid for measuring the legend duration of SSRI and other antidepressant exposures among older people. Specifically, the assumption of a daily dose of one unit led to misclassification of the prescribed dose in 13.1% of the SSRI prescriptions and in 25.3% of the other antidepressant prescriptions. The proportions of misclassification were higher for tricyclic antidepressants (53.8%), antipsychotics (57.6%) and benzodiazepines (79.9%), suggesting that the dosage assumption of one unit per day may lead to severe misclassification of a patient's exposure status.

Compared with the fixed-time window method and an intention-to-treat approach, the legend duration method is likely to achieve higher sensitivity and specificity as it estimates actual periods of drug exposure. In a case control study, for example, a patient's current exposure status can be defined by estimating whether the legend duration of the last prescription overlaps with the day of the outcome event (Wang *et al.*, 2001; Zint *et al.*, 2010). In a cohort study, respectively, the legend duration method can be used for identifying patients who discontinue use (Gill *et al.*, 2007) and for dividing the follow-up time into exposure and non-exposure periods (Tamblyn *et al.*, 2005; Ray *et al.*, 2009; Tiihonen *et al.*, 2009).

Although the dosage assumption of one unit per day appears valid for measuring the legend duration of SSRI and other antidepressant exposures among older people, it should be noted that misclassifications may still occur if a patient discontinues use before the package expires or if a patient is non-adherent (Schneeweiss and Avorn, 2005; Caskie and Willis, 2004). For instance, a recent Canadian study showed that every fourth antidepressant user aged ≥ 65 years had either missed a dose or taken less than a prescribed amount during a typical month over the past year (Bulloch and Patten, 2010). Because of non-adherent behaviour, researchers may underestimate the actual duration of a prescription and observe apparent treatment gaps between two consecutive prescriptions (Gardarsdottir *et al.*, 2010a). In order to avoid misclassification due to non-adherence, researchers may multiply the legend duration of the last prescription by a predefined factor, such as 1.1 (Lau *et al.*, 1997). In addition, researchers may define a maximum number of days that may elapse between two consecutive prescriptions for them to be considered as a single treatment episode (Gardarsdottir *et al.*, 2010b).

Despite the potential advantages of the legend duration method, the dosage assumption of one unit per day cannot

Figure 2 The overall proportions of misclassified antidepressant prescriptions when assuming a daily dose of 1 unit by patient characteristics.

be recommended for estimating antipsychotic and benzodiazepine exposures among older people. Specifically, the dosage assumption may overestimate the actual duration of antipsychotic exposure for many patients, since about 40% of the prescriptions included a dose above one unit per day. Conversely, among benzodiazepines, the dosage

assumption may underestimate the actual duration of exposure since over half of the prescriptions were intended for "as needed" use. In addition, the legend duration method may fail to capture patients who purchase drugs for future use. The findings of our previous study suggested that some patients may initiate antipsychotic

Table 3 The percentages of prescriptions with a prescribed dose below or above one unit per day and defined daily dose (DDD) per day

		One unit per day ¹		DDD per day ²				
	<i>n</i>	Below %	Above %	Below %	Above %	DDD mg	MCPD mg	% ³
<i>Antipsychotics</i>								
levomepromazine	266	19.9	15.4	99.6	0.0	300	25	(42.9)
perphenazine	328	0.3	51.2	99.7	0.3	30	4	(32.0)
haloperidol	230	16.1	43.9	97.8	0.0	8	1	(35.2)
melperone	207	0.5	54.1	100	0.0	300	25	(24.2)
chlorprothixene	176	3.4	50.6	97.7	1.1	300	50	(30.7)
olanzapine	693	9.7	17.0	68.7	11.4	10	5	(47.9)
quetiapine	2469	5.9	49.7	97.9	0.8	400	25	(36.9)
risperidone	3387	23.0	28.0	99.7	0.2	5	0.5	(41.0)
<i>Benzodiazepines</i>								
diazepam	1211	23.0	14.0	85.1	3.6	10	5	(49.2)
chlordiazepoxide	130	13.1	36.2	82.3	8.5	30	10	(34.6)
alprazolam	1245	17.8	30.8	73.7	10.8	1	0.5	(35.3)
nitrazepam	558	26.9	7.2	26.9	7.2	5	5	(65.9)
oxazepam	5248	34.2	19.2	95.6	2.6	50	15	(43.5)
lorazepam	1639	17.9	35.9	86.9	12.0	2.5	1	(46.2)
temazepam	6445	32.4	4.7	49.9	3.9	20	20	(46.1)
zopiclone	16374	47.8	2.9	48.7	2.9	7.5	7.5	(48.4)
zolpidem	2592	51.5	1.6	51.5	1.6	10	5	(51.2)
<i>Antidepressants</i>								
amitriptyline	781	6.5	15.4	95.0	2.8	75	25	(70.4)
doxepin	522	1.9	26.8	92.9	2.5	100	25	(31.2)
fluoxetine	320	2.8	11.6	29.7	9.1	20	20	(61.3)
citalopram	4733	4.8	4.7	41.1	8.9	20	20	(50.1)
paroxetine	157	17.2	15.9	17.2	17.8	20	20	(65.0)
sertraline	424	16.3	10.6	15.6	21.2	50	50	(63.2)
escitalopram	2850	6.2	4.0	36.7	12.7	10	10	(50.6)
mianserin	427	8.0	18.3	80.3	4.7	60	30	(40.3)
mirtazapine	5514	20.2	3.4	64.0	5.8	30	15	(49.7)
venlafaxine	692	0.3	13.2	67.8	32.2	100	75	(54.8)
duloxetine	818	0.1	11.7	41.0	5.6	60	60	(53.4)

¹The percentages of prescriptions with a prescribed dose below or above one unit per day (if the prescription included a dose range, the minimum dose was considered).

²The percentages of prescriptions with a prescribed dose below or above the defined daily dose (DDD) per day (if the prescription included a dose range, the minimum dose was considered).

³The percentage of prescriptions with a prescribed dose of the most commonly prescribed dose in milligrams (MCPD) per day.

and benzodiazepine treatment several months after dispensing, since the sensitivity of the Finnish Prescription Register for identifying current users increased when the fixed-time window was extended from 6 to 12 months (Rikala *et al.*, 2010).

There are many potential explanations for the doses below and above one unit per day. Firstly, many psychotropic drugs, such as melperone, quetiapine, benzodiazepines

(when used as anxiolytic), moclobemide and amitriptyline combinations, are advised to be administered more than once a day (Finnish Medicines Agency, 2011). Secondly, the drug strengths available on the market may not be suitable for older people. In Finland, for example, the lowest strength available is 15 mg for oxazepam, 5 mg for zopiclone and 15 mg for mirtazapine. The limited availability of suitable drug strengths may also explain

the variation in the validity of the dosage assumption between indications. For instance, the lower validity of the dosage assumption among other antidepressants prescribed for insomnia may result from the fact that guidelines recommend a dose of 3.75 to 7.5 mg of mirtazapine for insomnia (Finnish Medical Society Duodecim, 2008), even though the lowest strength available is 15 mg. However, there are few possibilities to take indication into account in exposure assessment, since prescription registers do not typically include information on diagnoses or indication for use (Furu *et al.*, 2010).

Besides indication, the validity of the dosage assumption differed between new and prevalent users. Specifically, among new users of other antidepressants, one-third had a dose below one unit per day, suggesting that the dosage assumption may underestimate the legend duration of a first prescription, which should be taken into account in new-user designs (Ray, 2003). In addition, the validity of the dosage assumption was lower for those who purchased ≤ 30 units of other antidepressants and SSRIs than for those purchasing > 30 units. This difference may partly be due to the fact new users tend to purchase smaller quantities, whereas those with a longer history of use usually purchase drugs for a three-month period. However, the difference was seen in both new users and prevalent users, suggesting that a smaller quantity purchased is also an independent indicator of lower validity.

The DDDs are frequently used as a proxy for prescribed doses when measuring the legend durations of psychotropic drug exposures (Bak *et al.*, 2002; Tihihonen *et al.*, 2009; Modén *et al.*, 2010). However, the findings of our study indicate that older people tend to be prescribed psychotropic drugs with lower doses than those of the DDDs. Therefore, using the DDD as a proxy for prescribed dose is likely to underestimate the actual duration of drug exposure, potentially leading to exposure misclassification and biased measures of association. The potential consequences of this finding can be illustrated by an example. A nested case control study on the association between psychotropic drug use and falling accidents among people aged ≥ 65 years divided people into new users, current users, past users and non-users based on timing of exposure (Modén *et al.*, 2010). The timing of exposure was estimated using the date of purchase, quantity purchased and the DDD. Because the DDDs are likely to underestimate the actual duration of psychotropic drug exposure, some of those defined as non-users may have actually been either past users or current users, whereas some of those defined as past users may have actually been current users. Therefore, for instance, the odds ratios for falls

associated with past use and current use may have been biased towards the null.

Methodological considerations

The Finnish Prescription Register provided a great opportunity for nationwide analyses of dosing patterns of psychotropic drugs. The study population included people aged ≥ 75 years with at least one purchase of psychotropic drugs recorded in the Prescription Register in September 2009, being representative of the general community-dwelling older population. The number of prescriptions analysed was large enough for estimating the proportions of misclassification separately for subcategories of psychotropic drugs and for assessing the influence of patient characteristics on the proportions of misclassification. The dosing instructions were available for almost every prescription, increasing the validity and generalizability of the findings. Nevertheless, the findings of this study may not be fully generalizable to people aged 65–74 years due to potential differences in indications and usage patterns between age groups. Therefore, future studies should evaluate the validity of the dosage assumption of one unit per day in younger age groups as well.

This study has some limitations. Firstly, the study used prescribed doses as a proxy for actual doses. A prescribed dose may differ from an actual dose if a physician gives an oral instruction differing from the written one. For instance, there may be a need to increase or decrease the prescribed dose due to insufficient efficacy or adverse effects. Patients may also alter the medication regimen independently. Specifically, a study by Barat *et al.* (2001) revealed that people aged ≥ 75 years do not always follow the prescribed drug regimen. For instance, 58% of the participants used hypnotics with lower doses than prescribed and 58% took hypnotics less frequently than prescribed. Furthermore, some patients may use benzodiazepines on a daily basis, although intended for “as needed” use because of dependence (Ashton, 2005).

In this study, the prescriptions including a dose range were considered misclassified, because the legend duration of drug exposure cannot be calculated without specifying the exact dose. For example, with a prescribed dose of 1–2 units 1–3 times per day, the duration of a package of 100 units may range between 17 and 100 days. Because of this approach, however, the study may have overestimated the overall proportion of misclassification. Specifically, many of those who were prescribed psychotropic drugs with a dose range may actually have used one unit per day if this dose was within the minimum and maximum dose.

This study was further limited by the fact that the Prescription Register does not include information on non-reimbursable drugs, such as short-acting benzodiazepines and zaleplon. In addition, lower strengths of amitriptyline and small packages of doxepine, nirtazepam and temazepam were not covered by the data. Therefore, the study may have overestimated the MCPDs for these drugs. Furthermore, the study may have misclassified some of the prevalent users as new users if they had purchased non-reimbursable drugs during the six-month period preceding September 2009. In addition, the six-month window may have been too short to capture some prevalent users (Rikala *et al.*, 2010).

Conclusions

This study indicated that the dosage assumption of one unit per day is valid for measuring the legend duration of SSRI and other antidepressant exposures among people

aged ≥ 75 years. The validity was lower for antipsychotics, benzodiazepines and tricyclic antidepressants, suggesting that the dosage assumption of one unit per day is likely to lead to misclassification of patient's exposure status and thereby biased measures of association.

Acknowledgements

The study was funded by the Social Insurance Institution of Finland. In addition, financial support was obtained from the Graduate School of Ageing, Well-being and Technology, University of Jyväskylä, Finland. The authors are grateful to IT specialist Kristiina Tyrkkö and to statistician Piia Lavikainen for their assistance with the data construction and management.

Declaration of interest statement

All the authors declare that they have no competing interest.

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