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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Antiepileptic drug use in community-dwelling and institutionalized elderly: a nationwide study of over 1 300 000 older people

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Abstract
Purpose To investigate whether institutionalization is associated with the use of antiepileptic drugs (AEDs) and to compare the association between use of AEDs and psychotropics in community-dwelling and institutionalized elderly, after adjustment for age, sex and co-morbidity (i.e. number of other drugs).
Methods We analyzed data on age, sex and dispensed drugs for individuals aged ≥65 years registered in the Swedish Prescribed Drug Register from July to September 2008, record-linked to the Swedish Social Services Register (n=1 345 273: 1 258 565 community-dwelling and 86 708 institutionalized elderly). Multivariate logistic regression analysis was used to analyze whether institutionalization and use of psychotropics (i.e. antipsychotics, anxiolytics, hypnotics/sedatives and antidepressants) were associated with the use of AEDs.
Results AEDs were used by 2% of the community-dwelling and 9% of the institutionalized elderly. The most commonly used AEDs were carbamazepine, gabapentin, pregabalin, valproic acid and lamotrigine. Institutionalization was strongly associated with AED use ($OR_{adjusted}$=3.98; 95% CI 3.86–4.10). In community-dwelling elderly, AED use was associated with an increased probability of use of all types of psychotropics. However, among institutionalized elderly, the associations between use of AEDs and psychotropics showed a mixed pattern.
Conclusions AED use seems to be common among Swedish institutionalized elderly, and institutionalization is a strong determinant of AED use. Our results may also indicate an off-label prescribing of AEDs as an alternative to psychotropics in the institutional setting. This finding needs to be confirmed by others and evaluated with respect to outcomes of this treatment in institutionalized elderly.

Keywords Antiepileptic drugs · Community-dwelling · Drug register · Elderly · Institutionalization · Psychotropic drugs

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Introduction

The incidence of epilepsy and use of antiepileptic drugs (AEDs) increases with age [1–3]. Although the incidence of epilepsy is higher in the elderly older than 75 years than among younger populations [4], there has been comparatively little focus on epilepsy in older people [5].

AED therapy in old age is complicated. The tolerability of these drugs is lower in the elderly population due to age-related changes in pharmacokinetics and pharmacodynamics, frailty, co-morbidities and concomitant use of potentially interacting drugs. In fact, AEDs are among the drug classes most highly associated with adverse drug reactions in older people [6]. Also, few randomized clinical trials (RCTs) of AEDs have included people aged 75 years and older [7]. Taken together, it is recommended that caution should be taken when prescribing an AED to an elderly patient [6].

Nevertheless, AED use in the elderly seems to be common, particularly in institutions. Studies in the USA have reported a prevalence of AED use of about 10% in institutions [8–12], although the use of AEDs does seem to be lower in the European institutional setting [13, 14]. Studies on the use of AEDs among community-dwelling

elderly are scarce [15, 16]. To the best of our knowledge, there have been no studies comparing AED use in community-dwelling and institutionalized elderly, possibly due to the lack of sufficiently large databases. Therefore, in the study reported here, we used data from the Swedish Prescribed Drug Register record-linked to the Swedish Social Services Register, which enables extensive nationwide analyses of drug use in both community-dwelling and institutionalized elderly.

The risk of mental disorders [17, 18] and the use of psychotropics [19, 20] are higher in epilepsy patients. Therefore, one would expect a high correlation between the use of AEDs and psychotropics. However, we have been unable to identify any published study that has examined the association between AED use and psychotropics. Further, off-label use of AEDs for mental and neurological disorders appears to be common [21, 22], in particular in the elderly [22]. For example, AEDs are sometimes prescribed off-label for behavioral and psychological symptoms of dementia (BPSD)—despite the fact that AEDs are not indicated for use in this condition. Therefore, RCTs are needed to provide data for evidence-based recommendations [23].

The primary aim of our study was to investigate whether institutionalization was associated with the use of AEDs in the elderly Swedish population, after adjustment for age, sex and co-morbidity (i.e. use of other drugs). A second aim was to compare the association between AED use and psychotropics in community-dwelling and institutionalized elderly.

Methods

Study population

The Swedish Prescribed Drug Register contains individual-based data for all prescriptions dispensed to the whole population of Sweden (about 9 million inhabitants) [24]. We analyzed non-identifiable data from individuals aged ≥65 years who were registered in the Swedish Prescribed Drug Register from July to September 2008, with information on each individual's age, sex and dispensed drugs (amount of prescribed drug, when the prescription was filled and prescribed dosage according to the prescriptions written by the prescribers). After exclusion of the 0.2% of the population (2 291/1 347 564 individuals) with missing data on place of residence, the study population consisted of 1 345 273 older people (1 258 565 community-dwelling and 86 708 institutionalized elderly).

Information on the 3-month period about when the prescription was filled, the amount of drug and the prescribed dosage was processed to calculate the duration of drug exposure [25, 26]. The time period of 3 months was chosen based on the fact that in Sweden drugs are prescribed for use for at most 90 days. When data on the prescribed dosage were incomplete or missing (9.9%), we based our calculations of drug exposure on defined daily doses (DDDs) [27]. For each drug, the mean prescribed daily dose (PDD) [27] for regular use was calculated. In the few cases in which the PDD could not be calculated, we assumed 0.9 DDDs for regularly used drugs (based on calculations of the total mean value for regularly used drugs among the elderly in the study population). For drugs prescribed as needed, 0.45 DDDs (50% of 0.9 DDDs) was employed. For dermatological and eye preparations, 1 DDD was assumed [26]. A list of current prescriptions was constructed based on the calculations of the duration of drug exposures for each individual on the arbitrarily chosen date of 30 September 2008. If a patient was dispensed the same drug in different doses during the study period, this was counted as one dispensed drug.

The Swedish Social Services Register has national coverage of individual-based information about social services financed by Swedish municipalities, including institutional care for people aged ≥65 years [28]. Only a negligible amount of institutional care for older people falls outside the municipal system in Sweden. We record-linked the study population derived from the Swedish Prescribed Drug Register to the Swedish Social Services Register to obtain information about the living situation (i.e. community-dwelling or institution) on 30 June 2008.

Definitions

Antiepileptic drug use was identified according to the Anatomical Therapeutic Chemical (ATC) code [27] N03 [29]. We only analyzed those individual AEDs (within ATC-group N03) with >1000 users: carbamazepine, gabapentin, pregabalin, valproic acid, lamotrigine, phenytoin, clonazepam and phenobarbital.

The psychotropic drugs were antipsychotics (ATC-code N05A), anxiolytics (N05B), hypnotics/sedatives (N05C) and antidepressants (N06A) [30].

The study cohort was categorized into six age groups: 65–69 (reference), 70–74, 75–79, 80–84, 85–89 and ≥90 years. Living situation was defined as community-dwelling (own home) or institution (e.g. nursing home, sheltered accommodation). Number of other drugs, used as a proxy for overall co-morbidity [31], consisted of the number of dispensed drugs used by the person other than AEDs and the specific psychotropic under study. This variable was divided into four categories: 0–4 (reference), 5–9, 10–14, and ≥15 drugs.

This study was approved by the ethical board in Stockholm (dnr 2009/477-31/3).

Statistical analysis

Multivariate logistic regression analysis was used to analyze whether living situation was associated with the use of AEDs, after adjustment for age, sex and number of other drugs. We also performed separate multivariate logistic regression analyses of AED use in relation to concomitant use of antipsychotics, anxiolytics, hypnotics/sedatives and antidepressants in community-dwelling and institutionalized elderly, adjusted for age, sex and number of other drugs. The results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). PASW Statistics ver. 18 for Windows (SPSS, Chicago, IL) was used for the analyses.

Results

The mean age was 75.6 years (median 75, range 65–109 years) for community-dwelling elderly and 85.6 years (median 86, range 65–109 years) for the institutionalized elderly (Table 1). Fifty-seven percent of the community-dwelling group were women compared to 70% of the institutionalized elderly. The community-dwelling elderly used on average 4.3 drugs (median 4, range 0–40 drugs) compared to 7.2 drugs (median 7, range 0–30 drugs) among the institutionalized elderly.

AEDs were used by 2% of the community-dwelling and 9% of the institutionalized elderly (about 37 and 4% used as needed in community-dwelling and institutionalized elderly, respectively) (Table 2). The average PDD for AEDs was 0.61 for community-dwelling and 0.49 for institutionalized elderly. Of the AED users, 11% of the community-dwelling and 10% of the institutionalized elderly concomitantly used ≥2 AEDs. The five most commonly used AEDs were, in decreasing order, carbamazepine > gabapentin > pregabalin > valproic acid > lamotrigine; these were analyzed in more detail.

The multivariate logistic regression analyses (Table 3) showed that institutionalization was strongly associated with overall AED use (OR 3.98; 95% CI 3.86–4.10), after adjustment for age, sex and number of other drugs. Institutionalization was also associated with the use of all individual AEDs, in particular with valproic acid (OR 6.66; 95% CI 6.12–7.26) and carbamazepine (OR 5.62; 95% CI 5.32–5.94). Age was inversely associated with AED use, except for gabapentin. Also, male gender was associated with overall use of AEDs and with carbamazepine and valproic acid use, whereas female gender was associated with the use of pregabalin. In addition, the use of many other drugs increased the likelihood of AED use, particularly the use of gabapentin and pregabalin.

Table 4 shows the results of the multivariate logistic regression analysis of the relation between concomitant use of AEDs and psychotropics in community-dwelling and institutionalized elderly, after adjustment for age, sex and number of other drugs. In community-dwelling elderly, AED use was associated with an increased probability of use of all types of psychotropics, with particularly strong associations between antipsychotics and valproic acid (OR 9.84; 95% CI 8.86–10.92) and lamotrigine (OR 9.41; 95% CI 8.40–10.55). However, among institutionalized elderly, the associations between use of AEDs and psychotropics were mixed. For example, the use of gabapentin was negatively associated with the use of antipsychotics (OR 0.54; 95% CI 0.46–0.63). In addition, neither the use of carbamazepine nor of valproic acid was associated with the use of any of the types of psychotropics. These associations were not explained by a lower use of psychotropics among the institutionalized elderly, as psychotropic drug use was much more frequent among the latter population than among their community-dwelling counterparts (data not shown).

Discussion

Main findings

In our nationwide population of older people, AEDs were used by 2% of the community-dwelling and 9% of the institutionalized elderly. Our findings from the institutional setting is in line with those from U.S. institutions, where the reported prevalence of AED use is about 10% [8–12], but they are higher than those reported for Italian (4%) and German (5%) institutions [13, 14]. These divergent results may be caused by differences in data sources and assessment of AED use. Our higher prevalence might also be explained by our more recent dataset, i.e. from 2008, at

Table 1 Characteristics of the 1 258 565 community-dwelling and 86 708 institutionalized elderly in 2008

Characteristics of study cohort	Community-dwelling	Institution
Mean age (years)	75.6±7.5	85.6±7.2
Sex		
Men	545 353 (43.3)	25 813 (29.8)
Women	713 212 (56.7)	60 895 (70.2)
Mean number of dispensed drugs	4.3±3.2	7.2±3.6

Data are presented as the number (n) ± standard deviation (SD), or as the number with the percentage in parenthesis

Table 2 Antiepileptic drug use among the 1 258 565 community-dwelling and 86 708 institutionalized elderly in 2008

Antiepileptic drug use	Community-dwelling	Institution
AED use (total)	27 179 (2.2)	7 381 (8.5)
1 AED	24 152 (1.9)	6 643 (7.7)
≥2 AEDs	3 027 (0.3)	738 (0.8)
Use of individual AEDs		
Carbamazepine	7 525 (0.6)	2 386 (2.8)
Gabapentin	5 819 (0.5)	1 497 (1.7)
Pregabalin	5 052 (0.4)	1 195 (1.4)
Valproic acid	2 945 (0.2)	982 (1.1)
Lamotrigine	2 490 (0.2)	432 (0.5)
Phenytoin	2 278 (0.2)	619 (0.7)
Clonazepam	1 451 (0.1)	395 (0.5)
Phenobarbital	823 (0.1)	215 (0.2)

AED, Antiepileptic drug

Data are presented as the number (*n*) with the percentage in parenthesis

which time the newer AEDs, such as gabapentin and pregabalin, were in use in clinical praxis. On the contrary, the prevalence of AED use among the community-dwelling elderly in our study seems to be low in comparison with the limited amount of data previously published [16]. Further, in our study, institutionalized elderly received on average lower doses (as shown by PDD) and AEDs were prescribed less often as needed than their community-dwelling counterparts. These findings might reflect a protocol of cautious prescribing of AEDs to the frailest elderly and differences in indications and practice for prescriptions to institutionalized and community-dwelling elderly.

The first-generation AEDs carbamazepine and valproic acid were commonly used by the older people in our study, as also reported by others [5, 11, 14]. In comparison to the whole adult population, a previous Swedish study by Mattsson et al. of epilepsy patients aged ≥18 years reported that the older the patients, the less likely was the use valproic acid, lamotrigine and levetiracetam [29]. In our study of older people aged ≥65 years, levetiracetam was excluded because of the ≤1000 user criterion and valproic acid and lamotrigine were the fourth and fifth most commonly used AEDs. Also, similar to the study by Mattsson et al., we also found that the older the person, the less likely was the use valproic acid and lamotrigine.

Carbamazepine and valproic acid have a high risk of causing adverse drug reactions and have a substantial potential for interactings with other drug therapies [32, 33]. Second-generation AEDs (e.g. lamotrigine, gabapentin and pregabalin) have been reported to be better tolerated than carbamazepine in geriatric patients [33]. AED therapy initiated in individuals when younger might continue into old age, which causes elderly patients to use older types of AEDs with less favorable safety profiles [29].

However, the second-generation AEDs gabapentin and pregabalin were also commonly used among the elderly in our study, as also recently reported in other studies [16, 34].

Table 3 Adjusted odds ratios with 95% confidence intervals for antiepileptic drugs dispensed to 1 345 273 older people in 2008

Variables	Total AED use	Carbamazepine	Gabapentin	Pregabalin	Valproic acid	Lamotrigine
Age (years)						
65–69	Reference	Reference	Reference	Reference	Reference	Reference
70–74	0.93 (0.90–0.96)	0.97 (0.92–1.03)	0.99 (0.91–1.07)	0.87 (0.80–0.94)	0.84 (0.76–0.91)	0.83 (0.75–0.92)
75–79	0.85 (0.83–0.88)	0.84 (0.79–0.90)	1.06 (0.99–1.15)	0.82 (0.76–0.89)	0.71 (0.64–0.78)	0.69 (0.62–0.77)
80–84	0.73 (0.71–0.76)	0.68 (0.64–0.73)	1.00 (0.93–1.08)	0.72 (0.66–0.78)	0.53 (0.48–0.59)	0.55 (0.49–0.62)
85–89	0.60 (0.58–0.63)	0.51 (0.47–0.55)	1.01 (0.93–1.09)	0.64 (0.59–0.70)	0.38 (0.33–0.42)	0.40 (0.35–0.47)
≥90	0.41 (0.39–0.43)	0.32 (0.29–0.36)	0.89 (0.80–0.98)	0.49 (0.44–0.55)	0.17 (0.14–0.20)	0.21 (0.17–0.26)
Sex						
Men	Reference	Reference	Reference	Reference	Reference	Reference
Women	0.88 (0.86–0.90)	0.66 (0.64–0.69)	1.02 (0.97–1.07)	1.27 (1.20–1.34)	0.77 (0.72–0.82)	1.02 (0.95–1.10)
Living situation						
Community-dwelling	Reference	Reference	Reference	Reference	Reference	Reference
Institution	3.98 (3.86–4.10)	5.62 (5.32–5.94)	2.29 (2.15–2.44)	2.43 (2.26–2.61)	6.66 (6.12–7.26)	3.05 (2.71–3.42)
Number of other drugs						
0–4	Reference	Reference	Reference	Reference	Reference	Reference
5–9	2.16 (2.10–2.21)	1.80 (1.72–1.88)	3.02 (2.85–3.20)	3.19 (2.99–3.40)	1.85 (1.72–1.99)	1.99 (1.84–2.16)
10–14	3.76 (3.63–3.88)	2.41 (2.26–2.57)	7.09 (6.62–7.59)	7.51 (6.98–8.09)	2.33 (2.10–2.58)	2.68 (2.38–3.01)
≥15	5.27 (4.94–5.61)	2.39 (2.08–2.76)	11.50 (10.30–12.83)	12.06 (10.71–13.57)	2.06 (1.63–2.61)	2.76 (2.13–3.58)

Data are presented as the odds ratio (OR) with the 95% confidence interval (CI) in parenthesis

Table 4 Adjusted odds ratios[a] with 95% confidence intervals for psychotropics dispensed to 1 258 565 community-dwelling and 86 708 institutionalized elderly in 2008

Population/physchotropic use	Antipsychotics	Anxiolytics	Hypnotics/Sedatives	Antidepressants
Community-dwelling				
AED use	4.67 (4.45–4.90)	2.33 (2.25–2.41)	1.81 (1.76–1.86)	2.97 (2.89–3.05)
Carbamazepine	4.63 (4.25–5.05)	1.93 (1.79–2.07)	1.18 (1.11–1.25)	2.15 (2.02–2.27)
Gabapentin	1.25 (1.07–1.46)	1.76 (1.64–1.90)	1.95 (1.84–2.06)	2.86 (2.70–3.03)
Pregabalin	2.80 (2.49–3.15)	3.48 (3.25–3.72)	2.93 (2.76–3.11)	4.22 (3.98–4.48)
Valproic acid	9.84 (8.86–10.92)	2.10 (1.88–2.35)	1.70 (1.55–1.86)	2.90 (2.66–3.16)
Lamotrigine	9.41 (8.40–10.55)	2.81 (2.51–3.14)	2.15 (1.96–2.35)	3.71 (3.40–4.06)
Institutionalized elderly				
AED use	1.03 (0.97–1.09)	1.24 (1.17–1.31)	1.21 (1.15–1.27)	1.25 (1.19–1.31)
Carbamazepine	0.97 (0.88–1.07)	1.05 (0.96–1.16)	0.96 (0.87–1.04)	0.92 (0.84–1.00)
Gabapentin	0.54 (0.46–0.63)	0.99 (0.88–1.11)	1.32 (1.19–1.46)	1.54 (1.38–1.71)
Pregabalin	0.97 (0.84–1.11)	2.04 (1.82–2.30)	1.78 (1.58–2.00)	1.77 (1.57–2.00)
Valproic acid	1.09 (0.94–1.26)	0.94 (0.81–1.09)	1.06 (0.93–1.21)	0.99 (0.87–1.13)
Lamotrigine	1.34 (1.09–1.66)	1.32 (1.08–1.63)	1.26 (1.04–1.54)	1.36 (1.12–1.65)

Data are presented as the OR with the 95% CI in parenthesis. Reference groups are non-users of the respective AEDs

[a] Separate multivariate analyses adjusted for age, sex and number of other drugs

These drugs are used to treat both epilepsy and neuropathic pain. Pregabalin is also licensed for use in generalized anxiety disorder [32]. In addition, off-label use of these drugs in BPSD and mental disorders seems common [32, 35, 36]. Lamotrigine was only the fifth most commonly used drug, although this drug appears to be a well tolerated and effective AED in the elderly population [33].

Institutionalization was strongly associated with AED use, particularly with valproic acid and carbamazepine use, after adjustment for age, sex and co-morbidity. This finding might be explained by the higher risk of seizures in patients with dementia [37], who constitute a major part of the institutionalized elderly. However, it has been reported that only about 1.5% of patients with dementia have seizures [38]. The strong relationship between institutionalization and use of AEDs might instead be influenced by off-label prescribing of AEDs in this setting [23]. AEDs cannot be recommended for treating this condition until the results of RCTs show beneficial effects in relation to adverse drug reactions of these drugs [23].

Male gender and younger age were also associated with the use of AEDs, which is in line with previous published research [8, 10, 13]. However, the use of pregabalin was associated with female gender, which may reflect the situation that pain and anxiety is more common in women. The association between younger age and use of AEDs is surprising given that the incidence of epilepsy increases with older age [3]. This finding might reflect an under-treatment of epilepsy with advancing age [10].

We also explored the association between the use of AEDs and psychotropics, after adjustment for age, sex and co-morbidity. Previous studies have found that the use of psychotropics is frequent in epilepsy patients [19, 20]. We confirmed this finding in community-dwelling elderly. However, in the institutionalized group, the associations between AED use and psychotropics showed a mixed pattern. For example, carbamazepine and valproic acid were not associated with the use of psychotropics. This finding could reflect a wish to minimize polypharmacy in these frail elderly people. However, another and more worrisome explanation might be that AEDs are used as an off-label alternative to psychotropics in the institutional setting [23, 35, 36].

Limitations

The cross-sectional design of our study does not allow us to draw conclusions regarding causality. The Swedish Prescribed Drug Register does not include information about the underlying indications and diagnoses, such as epilepsy, for the prescription of drugs. We also lacked information on co-morbidities. However, we did control for a proxy for overall co-morbidity (i.e. number of other drugs) [31].

We analyzed data on 1 345 273 elderly people registered in the Swedish Prescribed Drug Register from July to September 2008, which corresponded to about 81% of the total population aged ≥65 years in Sweden (according to Statistics Sweden's census data from 30 September 2008). Further, the Swedish Prescribed Drug Register does not include data on over-the-counter drugs. However, all AEDs and psychotropics in our study are only available as prescription drugs in Sweden. Also, the register does not

include drugs used in hospitals or from drug storerooms, which may have led to an underestimation of drug use in the institutional setting.

Moreover, our method is based on the assumption that all current drugs were dispensed during the observed 3-month period due to the fact that drugs are prescribed for use for a maximum of 90 days in Sweden. Therefore, it is possible that we have disregarded drugs that were dispensed before the 3-month period and used at a slower rate than intended. At the same time, we might have included drugs that were dispensed during the 3-month period but discontinued prematurely. In addition, our method is based on interpretations of the dispensed drugs'dosages written by the prescribers as well as on assumptions about DDDs when information about dosage was incomplete or missing [25, 26].

Finally, a general limitation of studies on drug registers is that data may not adequately reflect actual drug use given that adherence to treatment can be low [39].

Conclusion

AED use seems to be common in institutionalized elderly, although these frail patients represent a high-risk group for adverse drug reactions and drug–drug interactions related to these drugs. Also, based on our study, first-generation AEDs carbamazepine and valproic acid are still commonly used in the elderly. However, the use of the second-generation AEDs gabapentin and pregabalin, which are approved for use in other indications besides epilepsy, is also frequent.

Institutionalization is a strong determinant of AED use, even after adjustment for differences in age, sex and co-morbidity between community-dwelling and institutionalized elderly. Moreover, our results might indicate an off-label prescribing of AEDs as an alternative to psychotropics in the institutional setting. This finding needs to be confirmed by others and evaluated with respect to outcomes of this treatment in institutionalized elderly.

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Conflict of interest The authors declare that they have no conflict of interest.

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