Antiepileptic drug use in a nursing home setting: a retrospective study in older adults

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Summary

The authors set out to examine qualitatively the use of antiepileptic drugs (AEDs) in a population of older adults in a nursing home setting, evaluating aspects such as specialist prescriptions and changes in dosage.

This retrospective prevalence study was carried out in a state-funded nursing home that provides care and rehabilitation for elderly people.

The first objective of the study was to determine the prevalence of AED use in this population. The second objective was to monitor AED dosage modifications during the fifteen-month study period, focusing on the safety and the tolerability of AEDs.

In the period of time considered, 129 of 402 monitored patients received at least one anti-epileptic therapy. The prevalence of AED use was therefore 32%. Gabapentin was found to be the most commonly prescribed drug, with a frequency of 29%, and it was used mainly for anxiety disorders, psychosis, neuropathic pain and mood disorders.

KEY WORDS: antiepileptic drugs, elderly patients, gabapentin, off-label.

Introduction

Antiepileptic drugs (AEDs) are widely used in the treatment of epilepsy, as well as in various other neurological and psychiatric disorders, such as neuropathic pain, migraine and bipolar disorder, while their use in further indications is under investigation (Rogawski and Löscher, 2004; Spina and Perugi, 2004; Johannessen Landmark, 2008). The role of various neurotransmitters in both antiepileptic and psychotropic effects is increasingly documented and may explain the utility of AEDs for psychiatric indications (Toczek et al., 2003; Sargent et al., 2000).

Italy, like other European countries, is currently witnessing an increase in the size of the elderly population (aged >65 years), as well as a growing tendency for the elderly to enter nursing homes (Rapporto Istat, 2014, <http://www.istat.it/it/archivio/120991>). Symptoms such as epilepsy, neuropathic and chronic pain, migraine and psychiatric disorders are often encountered in the elderly population, and off-label uses of AEDs for mental and neurological disorders appear to be common (Spina and Perugi, 2004; Katayama et al., 2014). The second generation of AEDs (gabapentin, pregabalin, lamotrigine, oxcarbazepine, topiramate) seem to show greater tolerability in the elderly, especially when compared with benzodiazepines, with which they share some therapeutic indications, i.e. for the more common psychiatric symptoms (anxiety, agitation and insomnia); they also show fewer side effects (exacerbation of mental confusion in the elderly, addiction, withdrawal, delirium, postural instability and consequent falls) (Spina and Perugi, 2004; Katayama et al., 2014). Many studies support off-label indications of AEDs (e.g. to control behavioral symptoms, anxiety), gabapentin in particular (Kulkarni et al., 2008; Moretti et al., 2003; Book and Myrick, 2005; Fukada et al., 2012).

Several studies in recent years have explored the use of AEDs, to treat epilepsy and other disorders, in specific populations or geographical areas (Rochat et al., 2001; Caplan et al., 2005; Poston et al., 2007; Davis et al., 2008), but there is still a lack of studies dealing with the use of AEDs in the elderly, particularly in nursing home settings.

A previous trial conducted in Varese, Italy, analyzed the correlation between polypharmacy and side

effects, focusing on falls in elderly people; polypharmacy seemed to be a widespread practice in many clinical settings, including nursing homes (Baranzini et al., 2009a). Against this background, it is necessary to assess the tolerability and safety of administering AEDs in elderly patients (Baranzini et al., 2009b; Olfson et al., 2015). This retrospective observational trial examines, qualitatively, the use of AEDs in an elderly population living in a nursing home in northern Italy.

The first objective of the study was to determine the prevalence of AED use in this population, also examining the reasons for the use of these drugs.

The second objective was to study patterns of AED use, recording, in particular, interruptions of treatment, drug changes and dosage modifications with reference to, after an initial three-month observation, a one-year period (20/11/2013 – 20/11/2014), and focusing on the tolerability and safety of AEDs.

Materials and methods

This retrospective prevalence study was carried out at the “Residenza Sanitaria Assistenziale (RSA) Fondazione Fratelli Molina” in Northern Italy, a publicly funded nursing home that provides care and rehabilitation for elderly people. The nursing home comprises four buildings, or units, and has about 450 beds. The units are heterogeneous in terms of architectural design, care protocols and number of beds. Since March 2000, a consultation-liaison project has been in place between this institution and the Division of Psychiatry of the Department of Clinical and Experimental Medicine of the University Insubria in Varese.

The medical records of all residents (a total of 402 patients) were consulted and data were collected for the 129 patients who, in the initial three-month observation period, were prescribed or already taking, at least one AED. The observation was then continued with reference to the subsequent 12 months.

The only selection criteria for inclusion in the study were to be a nursing home patient taking AED(s). For each patient included we evaluated:

- use of AEDs
- socio-demographic data
- medical data (polypharmacy)
- SOSIA rating scale scores.

The SOSIA rating scale classifies level of frailty using three dichotomous indicators of: mobility, cognitive/behavioral abilities, and the presence of comorbidities. The mobility indicator is based on the following items: “personal hygiene”, “walking”, “bed/chair transfer” and “strength”; cognition was estimated taking into account the items: “confusion/mental state”, “irritability/relationship state” and “restlessness/behavioral state”; the presence of comorbidities was calculated on the basis of the pathologies presented by each elderly subject. The indicator values were calculated by summing the scores of the individual items

and dichotomizing the result (mild or severe) on the basis of a default cut-off value. For the indicator of mobility, the cut-off value was arbitrarily set at 4: a score ≤ 4 was taken to indicate “severe” motor dependence. For the global cognitive ability indicator, the cut-off was set at 7.5: patients with a score > 7.5 were considered “severe”. Finally, comorbidity severity was established by taking a value > 16 to indicate “severe” comorbidity. The SOSIA classes range from 1 (the most frail) to 8 (the least frail) (Nebuloni et al., 2011). This scale was administered and evaluated by the nursing home’s internal physician.

The patients’ medical files, routinely updated by the internal physician and by external specialists, were the main source of information. The treatment received by the patients reflected normal clinical practice, without the use of a formal protocol.

Percentages, and mean and median values with standard deviation (SD) were used to summarize baseline information for all variables.

Continuous variables were compared between groups using t-tests. The results of t-tests were reported as mean differences with 95% confidence intervals and p-values.

Categorical variables were summarized as number and percentage per group. They were compared between groups using Fisher’s exact test.

The data analysis was performed using SPSS® 13.0 for Windows (SPSS® Inc, Chicago, IL).

The study was approved by the institutional review board of the Fondazione Fratelli Molina.

Results

During the time period considered, 129 out of 402 monitored patients received at least one AED therapy (a prevalence of 32%).

The patients receiving at least one AED therapy had a mean age of 79.05 years (± 10.7 SD) and an age range of 49–99 years; they did not differ significantly in age from the total population of residents (82.8 ± 2.4 SD). The treated patients comprised 47 males (29%) and 82 females (71%); the men had a mean age of 77.29 years (± 8.37 SD) and the women 79.79 years (± 11.53 SD). Details of their education, marital status and occupation are reported in table I.

Figure 1 shows the distribution of the AED-treated residents by SOSIA scale of frailty classes. The residents belonging to Class 2 (the largest proportion) accounted for about 32% of the total.

We evaluated the first indications for AEDs. In 44 patients, AEDs were first prescribed before admission to the nursing home and in the other 85 after admission. Epilepsy, psychiatric disorders, neuropathic pain and migraine and chronic pain were found to be the first reasons for the use of AEDs (Table II).

Epilepsy was the most frequent indication for the prescription of AEDs before admission. In accordance with literature data (Stephen and Brodie, 2000), ischemic stroke and subarachnoid hemorrhage were

the most common etiologies of diagnosed seizures among epileptic patients.

The AEDs prescribed after admission were mainly

Table I - Nursing home residents taking AEDs: distribution by education, marital status and previous occupation.

	%	n
Education		
- completed primary school	60%	77
- completed junior high school	8.4%	11
- completed high school	15%	20
- graduated	1.6%	2
- not specified	15%	19
Marital status		
- married	22.5%	29
- unmarried	17.1%	22
- separated	3%	4
- not reported	20.2%	26
- widowed	37.2%	48
Previous occupation		
- employed	56%	72
- unemployed	7%	9
- self-employed	1.7%	2
- housewife	14%	18
- registered disabled	2.3%	3
- entrepreneur	9%	12
- not reported	10%	13

issued by psychiatrists for: behavioral alterations in dementia, mood disorders, anxiety and psychosis.

The most commonly prescribed AED was gabapentin (29%), followed by carbamazepine (19%), lamotrigine (16%), valproate (14%), pregabalin (8%), phenobarbital (7%), topiramate (6%), phenytoin (5%) and levetiracetam (4%).

Carbamazepine, lamotrigine and valproate were found to be the AEDs most commonly prescribed in epilepsy, but lamotrigine and valproate were also used in the presence of mood disorders; gabapentin was more frequently prescribed for psychiatric disturbances, but was also used for neuropathic pain and in migraine prophylaxis. Pregabalin, topiramate and phenytoin were used in epilepsy and in migraine, while levetiracetam was used exclusively in epilepsy and was prescribed only before admission because it was not available in the nursing home pharmacy (the patients who did use it procured it themselves). Figure 2 shows the distribution of indications for the most frequently prescribed AEDs.

With reference to the study period, we collected data on AED prescriptions and any adjustments of AED dosage (Table III); we also evaluated the reasons for these adjustments.

The symptoms responsible for AED use and for changes in the dosages, were grouped into five broad categories:

1. Sleep disorders: insomnia and sleepiness
2. Behavioral changes: anxiety, hyperorality, bizarre behavior, confabulation, bustling, impulsive behavior,

Figure 1 - Nursing home residents taking AEDs: distribution by SOSIA scale of frailty classes.

Figure 2 - Distribution of indications for AEDs.

Table II - AEDs: first indications before and after nursing home admission, by gender and as a proportion of all AED use.

	Epilepsy	Psychiatric disorders	Neuropathic pain	Migraine and chronic pain	Not reported
Before admission (34%, 44)	45%, 19	20%, 9	17%, 8	9%, 4	9%, 4
After admission (66%, 85)	38%, 32	42%, 36	13%, 11	7%, 6	-
Gender distribution, m/f	63%/37%	13%/87%	20%/80%	32%/68%	25%/75%
All AED users	39%, 51	35%, 45	15%, 19	8%, 10	3%, 4

reactivity, making strong claims, polemical attitude, anger, restlessness, agitation, aggression

3. Psychotic symptoms: delusions, hallucinations, persecutory experiences

4. Mood disorders: including depression, mood deflection, dysphoria, sadness, guilt, feelings of inadequacy, anxiety, manic symptoms, ruminations, emotional incontinence, dissatisfaction

5. Somatic-neurological symptoms: epilepsy, somatic complaints involving difficulty walking, neuropathic pain, migraine.

Since, as mentioned, psychiatric disturbances made up a large percentage of the first indications for AED use after admission, many and detailed psychiatric symptoms were reported.

During the second observation period (20/11/2013 to 20/11/2014), we found a total of 307 dosage changes: 208 increases and 99 reductions in dosage. First prescriptions were excluded from this calculation as they were not considered variations. There were also 66 interruptions of AED treatment, where the AEDs were either replaced by another molecule or simply discontinued (data not presented).

Changes in dosages of AEDs appeared to be significantly correlated with sleep disorders ($p=0.002$), behavioral changes ($p=0.004$) and somatic-neurological symptoms ($p=0.004$). Evaluating the individual symptoms within the subcategories showing the closest correlations with dosage changes, we noted a significant relationship with aggression ($p=0.019$), observed in 11 patients (6.4%) following an increase in the dosage and in one (0.9%) after a decrease, and sleep disorders with sedation appearing in four cases following a dose increase (2.3%) and in 21 following a decrease (18.6%). This explains why AEDs were increased in cases of agitation and behavioral changes; instead, in cases of insomnia we found no association with increased drug dosages: AEDs were not found to be indicated for hypnotic use. Evaluation of the somatic-neurological disorders revealed a relationship between pain and dosage changes ($p=0.032$), in this case 13 increases (7.6%) and two reductions (1.8%).

Of the patients prescribed AED dosage increases, 15.7% ($n=27$) were treated with at least one other AED therapy, while polypharmacy (≥ 4 drugs) (Baranzini et al., 2009b) was present in 24.6% ($n=28$) of those prescribed dosage reductions; we recorded a total of 55 (19.2%) changes in polypharmacy regimens.

Gabapentin was the most commonly used AED. In 79% ($n=30$) of cases it was introduced in the RSA ($p=0.002$), whereas it had already been prescribed prior to admission in only 21% ($n=7$).

After admission, gabapentin was prescribed to 53.8% ($n=20$) of patients by a psychiatrist, to 22.5% ($n=8$) by the RSA internal physician, to 15% ($n=6$) by a neurologist; in 8.8% ($n=3$) of cases the prescribing physician was not specified, and in one case it had been suggested by a palliative specialist.

Frequent psychiatric indications for the prescription of gabapentin were psychotic disorders ($p=0.007$), depression ($p=0.010$), neuropathic pain ($p=0.005$) and anxiety ($p=0.010$).

The dosage of gabapentin was in the range of 150–450 mg daily.

We focused on gabapentin because it was the drug found to be most frequently adjusted. A significant relationship emerged between sleep disorders (insomnia) and reduction of gabapentin ($p=0.004$). An increase in the dosage of gabapentin was also significantly linked to behavioral changes ($p=0.011$) and somatic-neurological disorders ($p=0.029$). There are more than 30 clinical trials evaluating the potential roles of gabapentin in postoperative analgesia, preoperative anxiolysis, and prevention of chronic post-surgical pain (Kong and Irwin, 2007), therefore we can say that the prescription of gabapentin by neurologists and psychiatrists was congruous with literature data. With regard to the issues of safety and tolerability, the incidence of any treatment-emergent adverse event (TEAE) was found to be 15% ($n=19$). Table IV lists the TEAEs related to the different AEDs.

The most frequent TEAEs were nausea, confusion and drowsiness. In only one patient prescribed gabapentin were urea and creatinine values found to

Table III – AED dosages during the first three months and during the follow-up.

AED	Dosage for first 3 months	AED dosage adjustments during next 12 months
Gabapentin	150–450 mg/day	± 150–300 mg/day
Phenobarbital	50–100 mg/day	± 50–100 mg/day
Pregabalin	75–225 mg/day	± 25–150 mg/day
Carbamazepine	300–600 mg/day	± 100–200 mg/day
Valproate	400–600 mg/day	± 100–300 mg/day
Phenytoin	230–400 mg/day	± 100–250 mg/day
Levetiracetam	500–750 mg/day	± 100–300 mg/day
Lamotrigine	100–200 mg/day	± 50–200 mg/day
Topiramate	100–400 mg/day	± 100–200 mg/day

be increased. Consequently the treatment was discontinued.

Discussion

The sample evaluated comprised 129 patients, mainly women, with an average age of 79.05 years (± 10.7 SD); 37.2% were widowed.

AEDs were used in 32% of the sample, a rate that differs from those reported by Garrad et al. (2000, 2003), Timmons et al. (2003) and Galimberti et al. (2016), who respectively reported estimated prevalence rates of 10.5-11%, 17% and 12.8% in elderly patients, but similar to those of Hying et al. (2006) whose data showed that AEDs were not indicated in more than 30% of patients.

The first objective of this study was to determine the prevalence of the use of AEDs, and this was found to be 32%.

Of the 129 AED users in our study, 39% had a diagnosis of epilepsy. This confirms the previous finding that the presence of seizures as an indication for AEDs was the main factor associated with the use of these drugs across elderly nursing home residents (Garrad et al., 2000, 2003, Galimberti et al., 2006).

In accordance with Hauser et al. (1991), the incidence of epilepsy in our trial was higher in the males than in the females, with the greatest gender discrepancy found after the age of 60 years; Galimberti et al. (2016) recently confirmed these findings, showing that seizures were reported more commonly in males than in females (7.9% vs 4.7%, $p=0.0064$).

We found that carbamazepine, lamotrigine and valproate were the AEDs most commonly used among patients with epilepsy. These findings are in line with those of Johannessen Landmark et al. (2009) and demonstrate an increased use of new AEDs (lamotrigine and valproate). A survey of outpatient facilities within the U.S. Department of Veteran Affairs (www.hsrd.research.va.gov/research/abstracts.cfm?pproject_id=2141695172) revealed that newly diag-

nosed elderly patients were more likely to receive gabapentin or lamotrigine; nevertheless the use of carbamazepine suggests that changes in practice patterns may be difficult and also determined by the chronological availability of the products — levetiracetam was used by only a small proportion of our epileptic patients because it was not present in the nursing home pharmacy —, and by knowledge of the products, and ideas about relative efficacy.

In our study there was a great prevalence of AED use for psychiatric indications (35% of AED users). This result may be due to different factors: the increasing use of AEDs for mood disorders and for behavioral alterations, and the presence of a psychogeriatric unit in the nursing home that provided the setting for the study. This finding was also confirmed by Galimberti et al. (2016) whose recent reappraisal study, conducted 12 years after a first survey of AED use in nursing home residents, found that the prevalence of AED use was three-fold higher than in the earlier study (12.8% vs 4.3%), possibly reflecting a generalized increase in the use of AEDs for non-epilepsy indications in nursing home facilities (Galimberti et al., 2016; Garrad et al., 2003; Hying et al., 2006; Timmons et al., 2003). Gabapentin was found to be the AED most commonly prescribed for psychiatric disorders. Gabapentin and other AEDs may be particularly effective in treating symptoms of labile affect, impulsivity and aggression. Gabapentin is structurally related to the central nervous system inhibitory neurotransmitter γ -aminobutyric acid (GABA), although it has no GABA mimetic action. In the geriatric population, gabapentin has the advantages of limited adverse effects (sedation), and a favorable pharmacokinetic profile (Bruni, 1996). The drug is not protein bound, does not interfere with hepatic metabolism, and has no clinically significant pharmacokinetic drug interactions (e.g., enzyme induction). It is, however, renally eliminated, and dosage reductions are necessary in patients with renal insufficiency (Miller, 2001). In accordance with these scarce adverse effects, no relationship between gabapentin use and sleep disorders emerged in our trial.

Table IV - Treatment-emergent adverse events related to AEDs.

AEDS	n (%)	TEAEs
valproate	4 (21%)	tremor, confusion, nausea
carbamazepine	4 (21%)	dizziness, drowsiness, fatigue
gabapentin	3 (16%)	nausea, dyspepsia, increased urea and creatinine values
lamotrigine	3 (16%)	dizziness, constipation, headache
topiramate	2 (11%)	blurred vision, drowsiness
levetiracetam	1 (5%)	restlessness
phenytoin	1 (5%)	confusion
phenobarbital	1 (5%)	nausea
pregabalin	0	

Abbreviations: TEAEs=treatment-emergent adverse events; AEDs=antiepileptic drugs

Contrary to these data we have also found trials describing a limited use of gabapentin, related to its reputation for low efficacy in intellectually disabled patients (Huber and Tomka-Hoffmeister, 2003) or suggesting a greater use of lamotrigine, levetiracetam and topiramate (Carpay et al., 2009). Several other AEDs are investigated for their potential role in anxiety, bipolar disorder and schizophrenia (Johannessen Landmark, 2008).

Unlike what was observed in the patients with epilepsy, the majority (87%) of our patients with psychiatric disturbances were females, while 13% were males.

An important limit of our trial is linked to the fact that some new AEDs were not available in the RSA pharmacy: levetiracetam, despite being a novel AED approved for use in treatment of partial seizures with or without secondary generalization, and having a favorable pharmacokinetic profile and a low potential for drug interactions (Abou-Khalil, 2008; Palermo et al., 2013), was used by only 4% of our patients, who procured it themselves.

The AEDs most commonly used for migraine and neuropathic pain were gabapentin and valproate. Topiramate was also used for migraine prophylaxis but less than the other drugs, probably due to its reputation for showing increased toxicity in this patient population (Huber, 2002).

The second objective of this study was to monitor the use of AEDs in this elderly nursing home population. The drug most frequently prescribed was found to be gabapentin (29%) and it was introduced mainly to treat anxiety disorders, psychosis, neuropathic pain and mood disorders. During the follow-up, we observed a reduction of evening doses of gabapentin: this finding could be a consequence of this drug's lack of sedative properties. A previous study of the elderly in northern Italy (Baranzini et al., 2009a), conducted within the same nursing home, indicated that the risk of sedation and falling is elevated with the use of certain drugs such as benzodiazepine. In our study, AED dosage increases were prescribed in cases with behavioral disorders and somatic-neurological disorders, suggesting that this treatment is preferred in patients with somatic problems that include walking difficulties.

The widespread off-label use of AEDs, particularly gabapentin, in elderly patients presenting with symptoms such as anxiety, confabulation, reactivity, making strong claims, polemical attitude, restlessness and agitation, appears to be motivated by evidence that patients show higher tolerance to its side effects compared to those associated with the usually recommended drugs such as benzodiazepine. With regard to the safety and tolerability of these drugs we noted that prevalence of TEAEs was 15%; the most frequent adverse events were nausea, confusion and drowsiness. Gabapentin, in this preliminary study, was not seen to produce significant side effects: this could provide a direction for future studies on reducing the risk of falls among the elderly in nursing homes (Tinetti, 2003). We observed increased values of creatinine

and urea in only in one patient and in this case the treatment was discontinued.

As already indicated, an important limit of our trial is the limited number of AEDs available within the Fondazione Fratelli Molina pharmacy, which does not reflect current use of these drugs across all settings. A further limitation, in addition to the retrospective nature of the study, was the sample size. However, we plan to conduct another study including elderly people from different contexts.

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