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Indications of newer and older anti-epileptic drug use: findings from a southern Italian general practice setting from 2005–2011

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- In recent years there has been a growing trend in anti-epileptic drug (AED) use, but limited data concerning AED indication of use are available in general practice.
- Various AEDs, including newer agents, have been approved for indications other than epilepsy and are increasingly used also for unlicensed indications.
- Valproate is the most commonly used AED for mood disorders. However lamotrigine has exhibited the most remarkable increase in use in recent years.

WHAT THIS STUDY ADDS

- The increasing use of newer AEDs is mostly due to the treatment for indications other than epileptic disorders, in particular neuropathic pain.
- Reimbursement restrictions have influenced newer AED use, particularly the use of pregabalin and gabapentin.
- The rise in AED prescriptions for mood disorders seems to be related to the increasing use mainly of valproate but also of lamotrigine as mood stabilizers.

AIMS

The aim of the study was to analyze the prescribing pattern of both newer and older AEDs.

METHODS

A population of almost 150 000 individuals registered with 123 general practitioners was included in this study. Patients who received at least one AED prescription over 2005–2011 were identified. The 1 year prevalence and cumulative incidence of AED use, by drug class and individual drug, were calculated over the study period. Potential predictors of starting therapy with newer AEDs were also investigated.

RESULTS

The prevalence of use per 1000 inhabitants of older AEDs increased from 10.7 (95% CI10.1, 11.2) in 2005 to 13.0 (95% CI12.4, 13.6) in 2011, while the incidence remained stable. Newer AED incidence decreased from 9.4 (95% CI 8.9, 9.9) in 2005 to 7.0 (95% CI 6.6, 7.5) in 2011, with a peak of 15.5 (95% CI 14.8, 16.1) in 2006. Phenobarbital and valproic acid were the most commonly prescribed AEDs as starting therapy for epilepsy. Gabapentin and pregabalin accounted for most new pain-related prescriptions, while valproic acid and lamotrigine were increasingly used for mood disorders. Female gender (OR 1.36, 95% CI 1.20, 1.53), age ranging between 45–54 years (OR 1.39, 95% CI 1.16, 1.66) and pain as an indication (OR 16.7, 95% CI, 13.1, 21.2) were associated with newer AEDs starting therapy.

CONCLUSIONS

Older AEDs were mainly used for epileptic and mood disorders, while newer drugs were preferred for neuropathic pain. Gender, age, indication of use and year of starting therapy influenced the choice of AED type. The decrease of newer AED use during 2007 is probably related to the restricted reimbursement criteria for gabapentin and pregabalin.

Introduction

Anti-epileptic drug (AED) treatment is the main therapeutic approach for managing epilepsy [1]. AEDs are traditionally classified as older or newer AEDs based on whether they have been marketed before or after 1991. Both these classes are heterogeneous in term of mechanism of action and pharmacological parameters, but the latter generally exhibit better tolerability and lower drug interaction risk [1]. In recent years, several epidemiological studies were conducted exploring AED utilization in general practice worldwide. These studies showed a growing trend in AED use [2–9]. However, there are very few studies concerning indication of use in this setting from 2005 onwards [6, 7, 9]. Moreover, not all AEDs are approved for the same indications and among newer AEDs, lacosamide and pregabalin are not indicated for the treatment of epileptic disorders as monotherapy. Many AEDs have been increasingly prescribed for indications other than epilepsy, such as a variety of neurological conditions and psychiatric disorders, resulting in important changes in their utilization [10, 11]. For example, valproic acid and topiramate were approved for migraine prophylaxis, gabapentin and pregabalin for neuropathic pain, while valproic acid, carbamazepine and lamotrigine were approved for the treatment of bipolar disorder [10, 12]. Indeed, in Italy all the AEDs are fully reimbursed by the National Health Service (NHS) not only for epilepsy but also for the above-mentioned indications. Nevertheless, as a result of the increasing use of pregabalin and gabapentin, from 2007 onwards, the NHS introduced a health policy measure (Nota 4), which restricted the reimbursement criteria of these two newer AEDs in non-epilepsy disorders for which scientific evidence has been provided [13]. Moreover, since newer AED treatment is more expensive and may be associated with adverse effects, it would be useful to identify predictors of newer AEDs as a choice of treatment. In light of these considerations, the aims of this study were: (i) to explore the prescribing pattern (as both 1 year prevalence and incidence) of newer and older AEDs from 2005 to 2011 in a general practice setting of Southern Italy and (ii) to characterize users of older and newer AEDs, assessing the rate and predictors of new treatment with newer AEDs with respect to older AEDs in the same population.

Methods

Data source

Data were extracted from the Arianna database which currently contains information about a population of almost 400 000 individuals living in the area of Caserta and registered with 289 general practitioners (GPs). Information collected includes patient demographics, clinical characteristics and drug prescriptions covered by the National Health Service (NHS), classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Every drug prescription is linked to medical diagnoses, which are coded by the International Classification of Diseases 9th revision (ICD-9). All participating GPs receive extensive training in data collection techniques. Data are recorded during routine clinical practice through dedicated software and transferred monthly to the central database in a fully anonymized way. Any data outside the established norms of quality and completeness were investigated and back-submitted to each participating GP in order to receive immediate feedback. GPs failing to meet these standard quality criteria were excluded from epidemiologic research according to the basic standards applied to pharmacoepidemiological research [14]. Data quality and completeness has been already validated in previous drug utilization studies [16, 17, 15-20]. The study was approved by the ethics committee of Messina University Hospital.

Study population

For this investigation, 123 GPs whose data met eligibility criteria during quality assessment from 2005–2011 were included. Among 168 397 individuals, aged ≥15 years and registered with these GPs, we identified those patients who received at least one AED prescription (ATC: N03*) during the observation years. Patients were included in the analysis irrespective of whether pharmacological treatment was initiated by GPs or by specialists working in the public or private sector. In fact, in Italy outpatients receive the medicines free of charge only through GP prescriptions.

Exposure

AEDs were classified in two groups. Individual AEDs and their ATC codes are reported below: (1) Older AEDs: phenobarbital (N03AA02), ethosuximide (N03AD01), phenytoin (N03AB02), valproic acid (N03AG01), carbamazepine (N03AF01), clonazepam (N03AE01), primidone (N03AA03), barbexaclone (N03AA40), valpromide (N03AG02); (2) Newer AEDs: levetiracetam (N03AX14), tiagabine (N03AG06), lamotrigine (N03AX09), gabapentin (N03AX12), topiramate (N03AX11), felbamate (N03AX10), oxcarbazepine (N03AF02), vigabatrin (N03AG04), pregabalin (N03AX16), lacosamide (N03AX18), rufinamide (N03AF03), zonisamide (N03AX15). All the above drugs were fully reimbursed by the Italian National Health Service for NHS-approved indications during the study period.

Data analysis

Demographic and clinical characteristics of each user and indication of AED use were analyzed, with specific focus on AED therapy. The 1 year prevalence of both older and newer AEDs treatment was calculated, for each calendar year, as the ratio of the number of patients

receiving at least one AED prescription and the number of subjects alive and registered in the GPs' lists in the same year.

To calculate the yearly incidence of AED use (cumulative incidence) a 'new user' was defined as a patient receiving a first AED prescription during the observation year, without any recorded AED prescription in the previous 365 days.

For each calendar year, the cumulative incidence was calculated as the ratio between the number of new users and the number of individuals alive and registered with the GPs and who were free from any AED prescription in the previous year. Both the yearly prevalence and incidence of AED use were expressed as rate per 1000 inhabitants (/1000 inhabitants), together with 95% confidence intervals (CI).

Statistical analysis

The Chi-square test was used to evaluate the variation in 1 year prevalence or incidence of AED use during the observation period. A two-tailed chi-squared test for categorical variables and Student's *t*-test for continuous variables with significance level of $P < 0.05$ were used to compare baseline characteristics of users of different AEDs according to AED class.

To identify predictors of starting treatment with newer AEDs compared with older AEDs, a univariate logistic regression model using older AEDs as comparators was used to assess the possible influence of age, gender, indication of use and year of starting therapy (crude OR). GP characteristics as gender, age, years from graduation, years of work within the NHS, their number of patients and the number of prescriptions they wrote during the study period were evaluated to understand the possible influence of these factors on the choice of AED. Moreover, all predictors that emerged as significant using the univariate model were included in a multivariate logistic regression model (adjusted OR). Odds ratios (ORs) with 95% confidence interval (CIs) were calculated for each covariate of interest.

Statistical analyses were performed using SPSS.20.0 (IBM Corp. SPSS Statistics).

Results

Characteristics of AED users

Out of a total sample of 168 397 individuals, 10 617 (6.3%) received at least one AED prescription during the period 2005–2011, of which 3832 (36.1%) and 8078 (76.1%) were older or newer AED users, respectively. In addition, 1293 (12.2%) patients received at least one prescription of both older and newer AEDs over the observation period. Demographic characteristics and indications of use are summarized in Table 1.

Users of newer AEDs were older, compared with users of older AEDs (54.6 ± 16.7 years *vs.* 50.0 ± 19.2 years) and were mostly female (59.0%, 95% CI 58.0, 60.1 *vs.* 50.8%, 95% CI 49.3, 52.4).

Among newer AED users, only 1153 (14.3%, 95% CI 13.5, 15.0) patients were treated for epileptic disorders

Table 1

Demographic characteristics of AED users stratified by AED group

	Newer AEDs† *n* = 8078			Older AEDs† *n* = 3832		
	n	**(%)**	**95% CI**	***n***	**%**	**95% CI**
Gender						
Female	4770	(59.0)	58.0, 60.1	1948	(50.8)	49.3, 52.4
Male	3308	(41.0)	40.0, 42.0	1884	(49.2)	47.6, 50.8
Mean age (± SD)	54.6	(±16.7)		50.0	(±19.2)	
Female	55.3	(±16.6)		52.6	(±18.9)	
Male	53.6	(±16.8)		47.4	(±19.2)	
Age groups (years)						
15–44	2366	(29.3)	28.3, 30.3	1640	(42.8)	41.2, 44.4
45–54	1401	(17.3)	16.5, 18.2	575	(15.0)	13.9, 16.1
55–64	1693	(21.0)	20.1, 21.9	562	(14.7)	13.6, 15.8
>64	2618	(32.4)	31.4, 33.4	1055	(27.5)	26.1, 29.0
Indications of use						
Epilepsy	1153	(14.3)	13.5,15.0	1716	(44.8)	43.2, 46.4
Pain	5648	(69.9)	68.9, 70.9	411	(10.7)	9.7, 11.7
Mood disorder	1050	(13.0)	12.3, 13.7	1495	(39.0)	37.5, 40.6
Other	227	(2.8)	2.4, 3.2	210	(5.5)	4.8, 6.2

†Users are not mutually exclusive for type of AEDs but are mutually exclusive for indications of use within AED group. AED, anti-epileptic drug; CI, confidence intervals; SD, standard deviation.

while 5648 (69.9%, 95% CI 68.9, 70.9) were treated for pain not otherwise specified (NOS). Pain NOS represents the indication of treatment in 71.0% (95% CI 69.7, 72.3) of females *vs.* 68.3% (95% CI 66.8, 69.9) of males ($P < 0.01$).

On the other hand, older AEDs were mainly used for epileptic disorders (44.8%, 95% CI 43.2, 46.4) or mood disorders (39.0%, 95% CI 37.5, 40.6) while only 10.7% (95% CI 9.7, 11.7) of patients were treated for pain using these drugs. For older AEDs as for newer ones, pain was the indication of use more commonly in females (12.7%, 95% CI 11.2, 14.2) than in males (8.7%, 95% CI 7.4, 10.0), ($P < 0.01$).

1 year prevalence of AED use

Overall, the prevalence of use increased slightly during the observational period from 22.8/1000 inhabitants (95% CI 22.0, 23.6) to 25.6/1000 inhabitants (95% CI 24.8, 26.4) ($P < 0.01$). The prevalence of older AED use increased from 10.7/1000 inhabitants (95% CI 10.1, 11.2) in 2005 to 13.0/1000 inhabitants (95% CI 12.4, 13.6) in 2011 ($P < 0.01$), while the prevalence of use of newer AEDs rose from 14.7/1000 inhabitants (95% CI 14.1, 15.3) in 2005 to 16.2/1000 inhabitants (95% CI 15.6, 16.9) in 2011 ($P < 0.01$), with a peak of 22.3/1000 inhabitants (95% CI 21.5, 23.0) in 2006 ($P < 0.01$) (Figure 1A). The same trend was observed stratifying by gender. Nevertheless, the male prevalence was slightly, although not significantly, higher among older AED users while newer AED prevalence of use was slightly, but not significantly, higher among females (Figure 1A).

1 year incidence of AED use

The cumulative incidence of any AED use decreased from 12.0 (95% CI 11.4, 12.6) per 1000 inhabitants in 2005, to

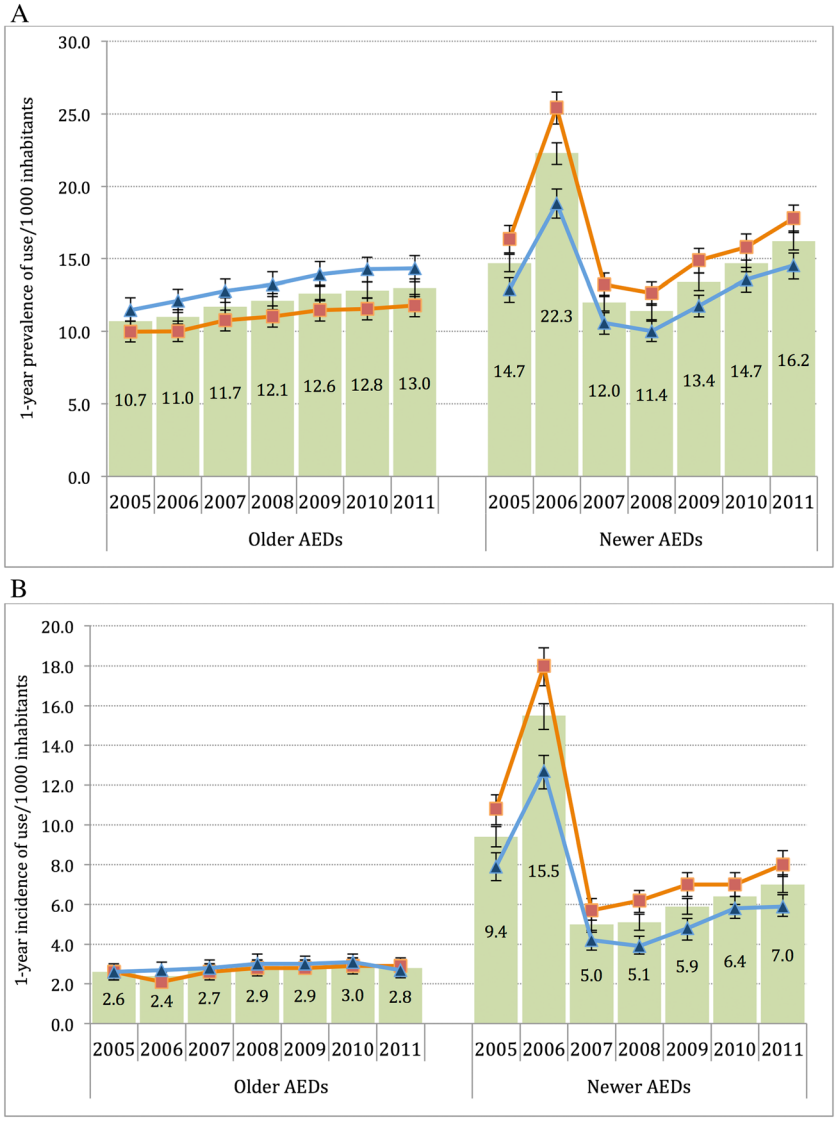

Figure 1

1 year prevalence (A) and incidence (B) of use of older and newer AEDs. , total; , female; , male

9.8 (95% CI 9.3, 10.4) in 2011 ($P < 0.01$). Nevertheless, the incidence of older AED users per year did not change significantly during the study period [2005: 2.6, 95% CI 2.3, 2.9; 2011: 2.8, 95% CI 2.5, 3.1 ($P = 0.28$)] (Figure 1B). In contrast, the cumulative incidence of newer AED users exhibited a peak from 2005 to 2006 [9.4, 95% CI 8.9, 9.9 *vs.* 15.5, 95% CI 14.8, 16.1 ($P < 0.01$)], followed by a fall in 2007 [5.0, 95% CI 4.6, 5.4 ($P < 0.01$ 2006 *vs.* 2007)] with a progressive rise until 2011 [7.0, 95% CI 6.6, 7.5 ($P < 0.01$ 2007 *vs.* 2011)] (Figure 1B).

Changes in the incidence of use for older and newer AEDs according to indication of use are summarized in Table 2. Most modifications seem to be related to the use of newer AEDs for neuropathic pain.

Phenobarbital and valproic acid were the AEDs primarily prescribed for epilepsy throughout the study period with no major changes in their prescribing pattern (Figure 2). However, the incidence of levetiracetam use increased from 0.4 (95% CI 0.04, 0.68) in 2005 to 2.3 (95% CI 1.52, 3.10) per 1000 inhabitants in 2011 ($P < 0.01$), while the incidence of carbamazepine and oxcarbazepine use slightly decreased from 1.9 (95% CI 1.15, 2.60) in 2005 to 1.0 (95% CI 0.52, 1.58) in 2011 ($P = 0.07$) (Figure 2A). Pain NOS newly-treated with AEDs was mainly managed with pregabalin and gabapentin and to a much lesser extent with carbamazepine or topiramate. Furthermore, neuropathic pain was the primary indication of use for these medications throughout the study period. The incidence of gabapentin use

Table 2

Incidence of use of newer and older AED by indication, stratified by calendar year

	Newer AEDs	95% CI	Older AEDs	95% CI
Epilepsy				
2005	7.3	5.9, 8.7	10.3	8.6, 12.0
2006	6.8	5.4, 8.1	9.9	8.2, 11.5
2007	5.7	4.5, 7.0	9.9	8.2, 11.5
2008	7.4	6.8, 8.0	9.4	7.8, 11.0
2009	7.5	6.1, 8.9	9.0	7.5, 10.6
2010	7.6	6.2, 9.0	8.7	7.2, 10.1
2011	7.1	5.7, 8.4	9.2	7.6, 10.7
Pain				
2005	76.0	71.5, 80.6	3.7	2.7, 4.7
2006§	134.8	128.7, 140.8	2.5	1.7, 3.3
2007¶	34.1	31.1, 37.1	3.1	2.2, 4.0
2008	34.2	31.2, 37.2	4.0	2.9, 5.0
2009	41.3	38.1, 44.6	3.6	2.7, 4.6
2010	46.2	42.7, 49.6	3.7	2.7, 4.7
2011††	50.9	47.2, 54.5	2.6	1.8, 3.4
Mood disorders				
2005	7.4	6.8, 9.0	10.9	9.2, 12.6
2006	8.9	7.4, 10.5	10.0	8.3, 11.6
2007	8.7	7.2, 10.2	12.3	10.4, 14.1
2008	8.7	7.2, 10.2	13.0	11.2, 14.9
2009	8.6	7.1, 10.1	14.6	12.6, 16.5
2010	9.1	7.5, 10.6	15.0	13.0, 17.0
2011†‡	9.8	8.2, 11.4	14.0	12.1, 15.9

†Newer AEDs $P = 0.03$ *vs.* 2005.‡Older AEDs $P = 0.02$ *vs.* 2005.§Newer AEDs $P < 0.01$ *vs.* 2005.¶Newer AEDs $P < 0.01$ *vs.* 2006.††Newer AEDs $P < 0.01$ *vs.* 2007.

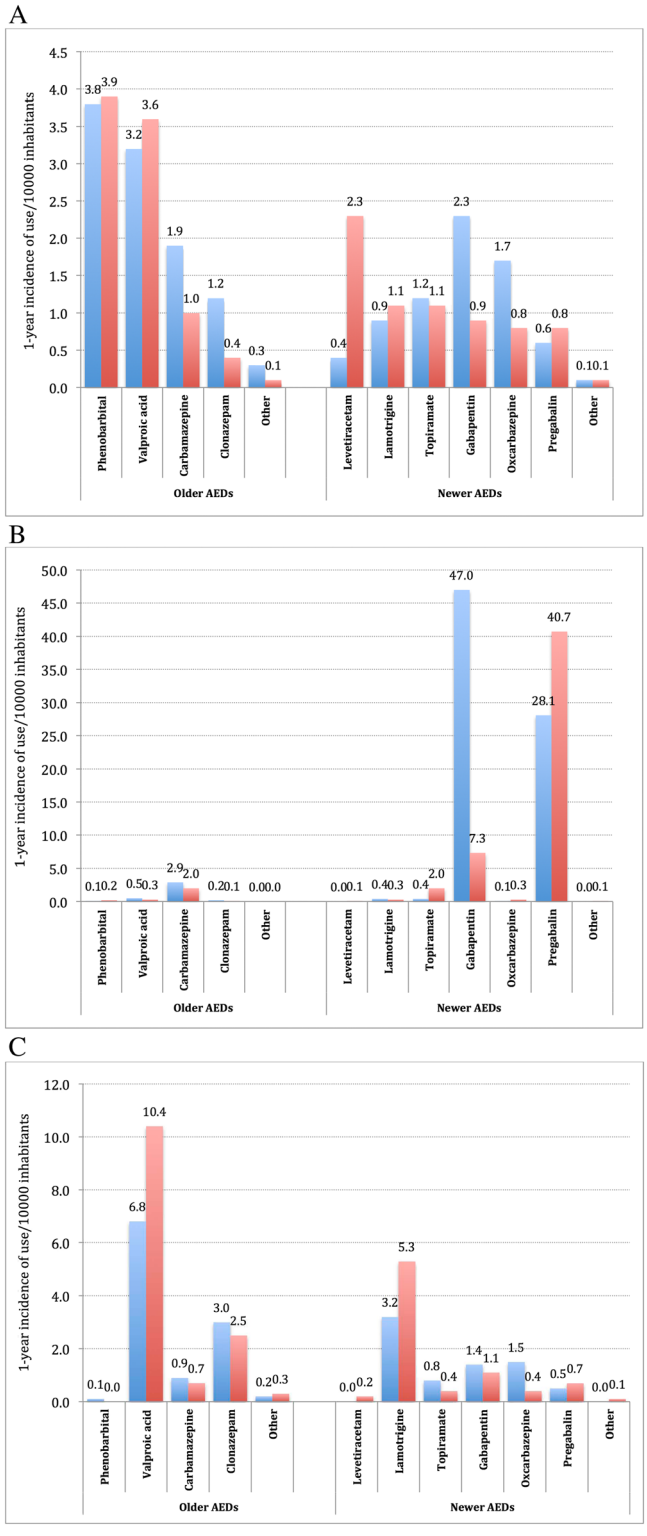

Figure 2

Incidence of use of AEDs by individual drug according to indication of use: Comparison between 2005 and 2011. Epilepsy (A), pain (B) and mood disorders (C). ■, 2005; ■, 2011

declined steeply from 47.0 (95% CI 43.4, 50.6) in 2005 to 7.3 (95% CI 5.9, 8.7) in 2011 ($P < 0.01$). On the other hand, pregabalin prescriptions rose from 28.1 (95% CI 25.3, 30.8) to 40.7 (95% CI 37.4, 44.0) ($P < 0.01$), with a peak of 99.1 (95% CI 94.0, 104.3) in 2006 (Figure 2B).

Valproic acid and lamotrigine were most commonly prescribed as starting therapy for mood disorders. The trend of use increased from 6.8 (95% CI 5.4, 8.2) in 2005 to 10.4 (95% CI 8.7, 12.1) in 2011 ($P < 0.01$) for valproic acid and from 3.2 (95% CI 2.3, 4.2) in 2005 to 5.3 (95% CI 4.1, 6.5) in 2011 ($P < 0.01$) for lamotrigine (Figure 2C).

Predictive factors for newer AED incident use

Characteristics of new users of AEDs and factors predicting newer AED use as starting treatment are summarized in Table 3 along with their respective crude ORs. In the univariate analysis, patients starting with a newer AED were more likely to be female (OR 1.46, 95% CI 1.33, 1.60, $P < 0.01$) and older than 45 years, compared with older AED users. Treatment for pain NOS was strongly associated with newer AEDs as drugs of first choice as compared with older AEDs (OR 25.4, 95% CI 22.2, 29.2, $P < 0.01$). The presence of epilepsy (OR 0.19, 95% CI 0.17, 0.22, $P < 0.01$) or mood disorders (OR 0.15 95% CI 0.13, 0.16, $P < 0.01$) was negatively associated with newer AEDs as starting therapy. In 2006, a general higher probability of starting treatment with a newer AED was seen (OR 1.83, 95% CI 1.55, 2.16, $P < 0.01$) compared with 2005, while this nearly halved in the period from 2007 to 2011. The significant associations with all the predictors evaluated in the univariate approach persisted in the multivariate logistic regression model (estimated as adjusted OR). Indeed, female gender, age over 45 years, pain as an indication and 2006 as the year of starting therapy are independently associated with a higher probability of starting treatment with a newer AED, while epilepsy, mood disorders and year of starting therapy from 2007 to 2010 are independently associated with a lower probability of starting with a newer AED (Table 3). GP characteristics such as gender, age, years from graduation, years of work within the NHS, their number of patients or the number of prescriptions written during the study period did not influence the choice of AED type.

Table 3

Predictive factors of incident treatment with newer AEDs compared with older AEDs

	Newer AEDs *n* = 6892 (%)	Older AEDs *n* = 2368 (%)	Crude OR (95% CI)	Adj. OR† (95% CI)	*P* value
Gender					
Male	2764 (40.1)	1169 (49.4)	Reference	1.36 (1.20, 1.53)	<0.01
Female	4128 (59.9)	1199 (50.6)	1.46 (1.33, 1.60)*		
Mean age, years (± SD)	55.4 (±16.1)	50.7 (±19.5)	1.016 (1.013, 1.019)*		
Mean age by gender, years (± SD)					
Male	54.7 (±16.0)	47.5 (±19.5)	1.024 (1.020, 1.028)*		
Female	55.8 (±16.2)	53.9 (±19.1)	1.007 (1.003, 1.011)*		
Age category (years)					
15–44	1862 (27.0)	994 (42.0)	Reference	Reference	
45–54	1225 (17.8)	328 (13.9)	1.99 (1.73, 2.30)*	1.39 (1.16, 1.66)	<0.01
55–64	1521 (22.1)	354 (14.9)	2.29 (2.00, 2.64)*	1.26 (1.06, 1.50)	<0.01
>65	2284 (33.1)	692 (29.2)	1.77 (1.57, 1.98)*	1.14 (0.98, 1.32)	0.08
Indication of use					
Epilepsy	644 (9.3)	840 (35.5)	0.19 (0.17, 0.22)*	0.77 (0.61, 0.97)	0.03
Pain	5319 (77.2)	278 (11.7)	25.4 (22.2, 29.2)*	16.7 (13.1, 21.2)	<0.01
Mood disorders	740 (10.7)	1077 (45.5)	0.15 (0.13, 0.16)*	0.68 (0.54, 0.86)	<0.01
Other	189 (2.7)	173 (7.3)	0.36 (0.29, 0.44)*		
Year of starting therapy					
2005	1305 (18.9)	361 (15.2)	Reference	Reference	
2006	2128 (30.9)	322 (13.6)	1.83 (1.55, 2.16)*	1.42 (1.16, 1.74)	<0.01
2007	641 (9.3)	350 (14.8)	0.51 (0.43, 0.60)*	0.75 (0.60, 0.93)	<0.01
2008	626 (9.1)	360 (15.2)	0.48 (0.40, 0.57)*	0.72 (0.58, 0.90)	<0.01
2009	710 (10.3)	345 (14.6)	0.57 (0.48, 0.68)*	0.88 (0.66, 1.00)	0.05
2010	734 (10.7)	334 (14.1)	0.61 (0.51, 0.72)*	0.80 (0.65, 0.99)	0.04
2011	748 (10.9)	296 (12.5)	0.70 (0.59, 0.84)*	0.97 (0.78, 1.20)	0.78

*$P < 0.01$ at univariate approach;†Adjusted for all predictors with a significant association at univariate approach. Values are shown as number (%) of new users, except where otherwise specified. Adj., adjusted; OR, odds ratio; SD, standard deviation.

Discussion

Drug utilization patterns of older and newer AEDs in Italy until 2005 were previously described by Alacqua *et al*. [7]. The current paper should be considered an update which builds on and expands the findings of previous studies [6, 7, 9].

The current study shows that the number of newer AED users from 2005–2011markedly exceeds that of older AED users (76.1% *vs.* 36.1%, respectively). Furthermore, newer AEDs were more commonly used in older and female patients. This is in agreement with several epidemiological studies carried out in other populations, suggesting an influence of age and gender in the pattern of use of AEDs[23–27]. Overall, the choice of starting treatment with a specific AED seems to be markedly influenced by the indication of use. While epilepsy and mood disorders remained the main indications of use for older AEDs, newer drugs were mainly prescribed for neuropathic pain. Similar findings have been reported in other population-based studies which suggest that the increasing use of newer AEDs is mostly due to treatment for indications other than epileptic disorders, in particular neuropathic pain [2-5, 9, 23, 25]. In Europe, gabapentin and pregabalin are extensively used for the treatment of neuropathic pain, as well as duloxetine and opioids. Moreover, the latter are also prescribed for a wide variety of non-neuropathic pain syndromes. However the National Institute for Health and Clinical Excellence (NICE) guidelines for neuropathic pain include pregabalin, which is preferred to gabapentin, as first line treatment. On the other hand, tramadol is only recommended as third line treatment, and evidence of efficacy of other opioids was found to be limited, making the benefit of these drugs for treating neuropathic pain questionable, also in view of considerable potential adverse effects [28].

In our study, the probability of starting treatment for pain with newer AEDs was over 16 times higher than with older AEDs. On the other hand, the probability of starting treatment for epilepsy or mood disorders was 23% and 32% lower for newer AEDs compared with older AEDs respectively.

As confirmed by other European studies, neuropathic pain is gradually becoming the primary indication of use for AEDs [24, 29] which could explain the increasing use of newer AEDs with increasing age, as found in this study. The higher female preponderance in newer AED utilization could be due to the treatment of female-dominated disorders such as pain syndromes [30]. However, in our study the probability of starting treatment with newer AEDs was higher in women and also in patients over 45 years, regardless of the indication of use. As a consequence, this peculiar pattern of use cannot be explained only by the higher prevalence of pain syndromes in these categories of patients.

Our results show that AED prevalence and incidence of use increased overall during the years 2005–2011. However, striking differences were seen between older and newer AEDs. The prevalence of older AED use increased progressively during the whole study period, while newer AEDs exhibited a peak in 2006, followed by a sudden fall in 2007 and then by a progressive increase until 2011. The increase shown in 2006 with respect to 2005 should be considered in view of the increasing trend observed since year 2000, as previously reported [7, 9], while the subsequent decrease in 2007 is likely to be attributable to the restriction of the national reimbursement criteria. When evaluating the incidence of use of older AEDs by single drug and according to indication, we found that prescriptions for mood disorders increased during the study period, while the incidence of use for epilepsy and pain remained stable. Phenobarbital and valproate were the most commonly prescribed drugs for epilepsy as previously found in the same setting [6, 7]. This suggests that in Italy, older compounds are often preferred to newer AEDs when the diagnosis is epilepsy. Moreover we confirmed the existence of the 'Italian anomaly', represented by the wide use of phenobarbital for epilepsy. The widespread use of phenobarbital in Europe, in contrast to the USA, is well documented in several epidemiological studies [9, 31]. This appears to be more evident in Italy [6, 7. 9]. Indeed, the widespread use of barbiturates conflicts with recently published international guidelines and expert consensus recommendations. This deserves particular consideration given the possibility of drug interactions and side effects in the elderly [6, 31-35]. On the contrary, phenytoin, a widely used AED in USA, is scarcely prescribed in the Italian general practice setting [7, 9]. Moreover, we noticed a progressive decrease in the incidence of carbamazepine use and the gradual rise of levetiracetam use. This could be explained by the fact that both drugs have a common indication, i.e. partial seizures, with the latter exhibiting higher tolerability. The incidence of use for pain disorders appears to be markedly influenced by marketing strategies and by National Health Service regulatory measures introduced in 2007 as well as revisions to such measures thereafter [13]. In fact, pain disorders were almost exclusively treated with gabapentin and pregabalin following these measures. Gabapentin and pregabalin, the most frequently prescribed newer AEDs, were highly prescribed until 2006, but exhibited a marked decrease after the endorsement of 'Nota 4' in 2007. Indeed, since that date, all AED prescriptions were always free of charge for all indications, while gabapentin and pregabalin were free only in epilepsy or severe neuropathic pain associated with post-herpetic neuralgia, diabetic neuropathy or cancer. The revision of the national reimbursement criteria in 2008 expanded the refundability of these drugs to the management of medullar lesions or post-stroke pain and neuropathic pain where

carbamazepine and tricyclic antidepressant drug therapy had failed or was contraindicated. This led to a progressive rise of pregabalin prescriptions until 2011. In line with the adopted regulatory measures, in our study the probability of starting treatment with newer AEDs rose more than 40% in 2006 compared with 2005 while in 2007 this dropped to 75%. Moreover, our results confirmed the mutually dependent trends of gabapentin and pregabalin use. The prescription pattern of these two drugs, marketed by the same manufacturer, is likely to be influenced by a promotional strategy as pregabalin was marketed in August 2004 when the gabapentin patent expired. Indeed, the decrease of gabapentin use since 2005 appears to be balanced by a parallel increase of pregabalin use [36, 37].

The rise in AED prescriptions for mood disorders seems to be related to the increased use of valproate and lamotrigine as mood stabilizers. In our study population, valproate overtook lamotrigine use. However, results from other studies only partially agree with our findings [38, 39]. Valproate is also the most commonly used AED for mood disorders in other populations, however its pattern of use appears to be stable while lamotrigine exhibits the most remarkable increase in recent years [23, 40, 41]. This is probably due to the lower teratogenic risk associated with lamotrigine use, resulting in this drug being preferentially prescribed to women with childbearing potential [25, 29, 30, 42]. Nevertheless, even if lamotrigine and valproate share a common indication for bipolar disorder, the former is not indicated for the acute maniacal phase of this disorder [38,39]. As a consequence, this could have induced physicians to choose preferably valproate in clinical practice due to possible advantages in the management of chronic treatment. Finally, as reported in a recent publication, there are several serious adverse drug reactions (ADRs) associated with the use of AEDs, such as suicide risk, fractures, birth defects, serious skin reactions and agranulocytosis [43]. Moreover, the same author [43] also revealed that age and gender influence the benefit/risk profile of AEDs. For example, lamotrigine seems to be more effective in males than in females. Although AEDs are well-known drugs, their extensive use in the treatment of epileptic disorders, mood disorders and pain, requires additional studies in order to improve the knowledge about efficacy and safety of such drugs and, at the same time, ensure patients' safety. Post-marketing surveillance activities, such as intensive monitoring drug studies [44, 45] are therefore important to allow the early detection of unexpected and/or serious adverse reactions, which have a considerable negative impact on both health and healthcare costs [46].

Limitations

The present study provides new information about the prescription patterns of older and newer AEDs in the Italian general practice setting. The availability of clinical information in the Arianna database allows the calculation of both prevalence and incidence of AED use associated with specific drug indications over long observation periods. In fact, to our knowledge, this is the first AED utilization study with 7 years of follow-up until 2011. Moreover, we were able to link several demographic and clinical characteristics to the type of AED chosen as starting therapy.

However some limitations should be considered. This study is based on prescription data, so we cannot ascertain whether the prescriptions were actually filled or whether the drugs were taken by the patient. Secondly, the clinical diagnoses made by GPs may not be accurate. It was for this reason that we decided not to evaluate AED use in the treatment of different subtypes of epilepsy. Moreover, only AED prescriptions linked to indications of use were analyzed. As a consequence, other pharmacotherapy prescribed for pain (opioids or other analgesics) or mood disorders was not considered in the analyses. However, this study was not aimed at exploring the prescribing pattern of drugs other than AEDs. Our analysis did not allow a precise temporal definition of repeated episodes of treatment with multiple drugs. Therefore, we were not able to differentiate between add-on treatment and switching between different AEDs. In addition, this study was carried out using data collected from a restricted area of Southern Italy. It is therefore possible that these findings are not fully generalized to the whole Italian general practice population. However, the comparison with the Italian national report on drug consumption supported the reliability of this database in providing information about AED drug utilization in Italy. Since we only included outpatients older than 15 years in the analysis, our results may not be generalizable to children, adolescents, elderly persons living in nursing homes and inpatients. To avoid underestimating AED use, only GPs who continuously provided high quality data to the Arianna database during the whole observation period were included in the study. A sensitivity analysis did not show any significant difference in prescribing behaviour between GPs enrolled in the study and the GPs not enrolled in the study, suggesting that our results are generalizable to non-participant GPs. Finally, we cannot exclude residual confounding factors of other underlying conditions.

In conclusion, the results of this study highlight relevant differences between older and newer AED trends of use. Older AEDs were mainly used in the treatment of epileptic and mood disorders while newer compounds were preferred for other indications, particularly for neuropathic pain. As reported previously, phenobarbital remains the most widely prescribed drug for epilepsy, despite not being recommended as first line therapy by recently published international guidelines.

Competing interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

Contributors

DI, ES and VA planned and designed the study. MT, DUT, MP, AA, AC, CR and CP analyzed the study data. DI, RF and VA drafted the manuscript. GT, JS, CF, AC and VA critically reviewed and approved the final manuscript.

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