Comparative effectiveness of eight antiepileptic drugs in adults with focal refractory epilepsy: The influence of age, gender and the sequence in which drugs were introduced onto the market

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Abstract

Objectives: The first objective was to determine the long-term retention rate of eight antiepileptic drugs (AEDs) commonly used as adjunctive therapy in adults with focal refractory epilepsy. Secondly, we assessed the effects of age and gender on retention rates. Thirdly, we examined if the retention rate could be influenced by the sequence in which the AEDs had entered the market.

Materials and methods: Patients with focal refractory epilepsy treated with any of the eight AEDs in Tampere University Hospital were identified retrospectively (N=507). Retention rates were evaluated with the Kaplan-Meier method. Follow-up started at the first date of treatment and each individual was followed a maximum of 36 months.

Results: We calculated the following three-year retention rates; lacosamide, 77.1% (N=137); lamotrigine, 68.3% (N=177); levetiracetam 66.7% (N=319), clobazam, 65.6% (N=130); topiramate, 61.6% (N=178); zonisamide, 60.4% (N=103); pregabalin, 54.6% (N=127); gabapentin, 40.2% (N=66). Lacosamide, levetiracetam and clobazam were the most effective AEDs in the elderly. The retention rate for pregabalin was higher in males (65%) than females (51%) whereas females had higher retention rates for both topiramate (72% vs. 58%) and zonisamide (67% vs. 57%). The retention rate was influenced by the sequence in which these AEDs entered the market.

Conclusion: We provide important information about practical aspects of these eight AEDs, revealing that there are differences in their effectiveness as adjunctive treatment for focal refractory epilepsy. Most importantly, the retention rate appears to be influenced by the sequence in which these AEDs were introduced onto the market.

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Introduction

Epilepsy is a chronic disorder that often requires lifelong treatment with antiepileptic drugs (AEDs). During the last decade, a new AED has been introduced for clinical use almost on an annual basis. This makes it increasingly difficult for the clinician to make a rational choice about which AED to select for which patient, especially in patients with drug-resistant epilepsy. It has been claimed that the choice of an AED is currently more empirical than evidence-based [1]. The tolerability and efficacy of new AEDs have been demonstrated in regulatory trials, but their strict entry and dosing criteria limit the amount of useful data that can be utilized in clinical practice [2].

Both the International League Against Epilepsy (ILAE) and the European Medicines Agency (EMEA) have emphasized the importance of gathering long-term retention data as a relevant endpoint for clinical trials of AEDs [3,4], since this provides information that can be applied readily to everyday practice [5]. The long-term retention rate of patients on their AED treatment is accepted as one of the clearest reflections of the drug's true therapeutic effectiveness (i.e. it combines aspects of efficacy and tolerability) [6].

Firstly, we evaluated the long-term retention rates for eight of the most commonly used AEDs as adjunctive therapy in our institution in patients with focal refractory epilepsy: clobazam, gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin, topiramate and zonisamide. Brivaracetam and perampanel were excluded from the analysis because they were not licensed in Finland at the time of this analysis, eslicarbazepine acetate because it was not fully reimbursed, and carbamazepine, oxcarbazepine and sodium valproate because they are extensively administered as the first-line therapy for new onset epilepsy [7]. The poor long-term retention rate for tiagabine (38.2%) in our center had been determined earlier based on an analysis conducted in 2004 [8]; since then, tiagabine has not been prescribed in our institution and therefore it was excluded from the current study. Vigabatrin was included in the early phase of the analysis, but excluded from the final analysis due to low number of cases (N=37).

Secondly, we assessed the effects of age and gender on retention rates of all eight AEDs due the fact that currently there is a lack of specific prescribing guidance for these subgroups of people with epilepsy [9].

It has been speculated, but not confirmed earlier, that the retention rate could be influenced by the sequence in which AEDs have been introduced into market [10]. Therefore, we analyzed each drug in terms of annual prescriptions and withdrawals from the introduction of the drug in Finland up to the final assessment point.

Materials and methods

Patients with focal refractory epilepsy (age ≥ 18 years) treated in Tampere University Hospital from January 1, 2004, to December 30th, 2014 were identified from the hospital patient registry using ICD-10 diagnostic codes for focal and unclassifiable epilepsy (G40.1X, G40.2X and G40.9). Refractory epilepsy was defined as having seizures after trials of at least two AEDs with maximally tolerated doses either sequentially or in combination therapy. However, patients ranging from 4-16% demonstrate only one prior AED in Table 1. To clarify, prior AEDs are defined as priory initiated and tapered off due to inefficacy in Table 1. In patients with one prior AED, the second AED failed to achieve complete seizure freedom, but it was continued due to clinical reasons (i.e. partial effect on seizure duration or frequency) and third AED was initiated as a combination therapy with the second AED. We included patients with focal refractory epilepsy who had ever used at least one of the following AEDs: clobazam, gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin, topiramate or zonisamide, (N = 507). All patients started these AEDs as adjunctive therapy. Overall, 21.9 % of the patients were treated with monotherapy, 43.0% with duotherapy, 29.7% with triple therapy, and 5.4% were being administered four AEDs. We retrospectively reviewed patient background, medical history, current and previous AED use, duration of therapy and reasons for treatment discontinuation. The etiologies were classified into either known (structural, metabolic, infectious) or unknown etiologies [11]. The majority of the refractory patients in the Tampere University Hospital district (population of 505 000) are monitored in our clinic and only some elderly as well as those patients with moderate or severe mental retardation are treated elsewhere.

The following classifications were made for the subgroup analyses. Age was categorized into two groups: <60 years of age and ≥60 years of age and the subjects were also subdivided by gender.

The background and medical characteristics of the patients are reported as means and ranges or proportions. The Kaplan-Meier method was used to obtain a product-limit estimate of the retention rate, and comparisons between the retention curves were analyzed using log-rank tests. Significance was determined as $p < 0.05$. Bonferroni correction was used for multiple comparisons. Follow-up started on the first date of treatment and each person was followed for a maximum of 36 months. Follow-up lasted until discontinuation of the treatment (event), death, or the end of the follow-up (range from 2 days to 36 months). All analyses were performed with Stata Statistical Software version 13.1.

Results

Clinical and demographic data on the patients treated with each AEDs are summarized in Table 1. Retention curves for all AEDs are presented in Figure 1. We estimated the following three-year retention rates; clobazam, 65.6%; gabapentin, 40.2%; lacosamide, 77.1%; lamotrigine, 68.3%; levetiracetam, 66.7%; pregabalin, 54.6%; topiramate, 61.6%; zonisamide, 60.4% (Table 2). Log-rank test showed significant variation between the AEDs (p=0.0001). In pairwise comparison lacosamide (p=0.003), lamotrigine (p=0.01), and levetiracetam (p=0.04) retention was significantly increased compared to gabapentin after Bonferroni correction. Other statistically significant differences between the retention rates could not be identified in pairwise comparison.

The reasons for discontinuation by those patients who terminated a particular AED within the three year follow-up period are shown in Table 3. The results of the subgroup analyses in which the patients were categorized according either to age or gender are summarized in Table 4. The annual number of initiations and discontinuations for lacosamide, levetiracetam, pregabalin, topiramate and zonisamide used as an adjunctive therapy in focal refractory epilepsy from 1995 to 2014 are illustrated in Figure 2.

Discussion

The most crucial finding in our study was that the retention rate appeared to be influenced by the sequence in which these AEDs were introduced onto the market and this "latest drug phenomena" should be taken into account when assessing the effectiveness of AEDs. Furthermore, we calculated the following long-term retention rates; lacosamide 77%, lamotrigine 68%, levetiracetam 67%, clobazam 66%, topiramate 62%, zonisamide 60%, pregabalin 55% and gabapentin 40%. All patients fulfilled the ILAE´s definition of pharmacoresistance [12].

An ideal study design should be relevant to real-world settings and provide encompassing measures of efficacy and tolerability assessed with reliable and valid tools. This requirement is usually not fulfilled in regulatory trials, which focus on efficacy and dose response in refractory patients. Often in these clinical trials, the dosage range tends to be high, the titration schedule too rapid and the follow-up period very short. In contrast, the retention rate is considered to be a compound measure of drug efficacy, safety and compliance, ultimately expressing the willingness of patient to take the drug.

It has been hypothesized that the retention rate can be influenced by the sequence in which these AEDs are introduced onto the market [10], but as far as we are aware, this has not been actually determined previously. In Finland, after authorities have given approval for full reimbursement, a new AED is made available free of charge for its licensed indication and the clinician can prescribe this drug to suitable patients. As shown in Figure 2, the use of a new AED significantly increases once full reimbursement is approved. Patients being administered AEDs that were marketed first could have discontinued that treatment after a new drug became available, as demonstrated in Figure 2. For example, topiramate entered the full reimbursement market in the year 2000; its peak of treatment discontinuations occurred in 2005 when a new AED (levetiracetam) became available. Similarly in 2007; many patients receiving levetiracetam terminated its use because of the availability of new drug (pregabalin). Finally, the number of annual discontinuations for pregabalin increased in 2008 when yet another AED (zonisamide) received full reimbursement approval. At the time of analysis, lacosamide was the latest AED which had been awarded full reimbursement (2012) and the peak of withdrawals from this drug had still not been observed by the end of year 2014. Additionally, lacosamide could have been tested in a more drug resistant cohort of patients. Our results suggest that the retention rate appears to be influenced by the sequence in which these AEDs have been introduced onto the market. This "latest drug phenomena" should be taken into account in the long-term retention rate studies, when comparing the effectiveness of subsequently marketed AEDs.

In the subgroup analysis, the effects of age and gender on retention rates of all eight AEDs were studied. Despite the well-known modifications in AED pharmacokinetics and pharmacodynamics in the elderly, we found only one retrospective, uncontrolled study of older patients (≥55 years) with epilepsy which would have evaluated effectiveness by comparing 12-month retention rates of 10 different AED [9]. In our study, lacosamide was the most effective AED in the elderly as measured by its three year retention rate, followed by levetiracetam and clobazam. Zonisamide and gabapentin were the least effective drugs. Our results are similar to those of Arif et al. [9] with one exception. In our study, lamotrigine had the third lowest retention rate (63%) in contrast to that previous study, in which lamotrigine had the highest retention rate (79%). The differences might be explained by the limited number of patients receiving each AED in both studies.

Surprisingly, very little is known about the effectiveness of AEDs between females and males in the light of long-term retention rate studies. We could not identify any study focusing on this topic. Three year retention rate for pregabalin was higher in males (62%) than females (53%) whereas females had a higher retention rate for both topiramate (70% vs. 56%) and zonisamide (68% vs. 57%). In fact, topiramate was the third best tolerated AED in females. However, results did not reach statistical significance due to limited number of patients. One might hypothesize that these results would reflect cosmetic side effects of AEDs to which females tend to be more prone, as pregabalin is associated with gaining weight whereas both topiramate and zonisamide might cause a loss of body weight [13].

The highest retention rate was found for lacosamide (77%), which is exactly the same percent as in prospective audit with adjunctive lacosamide in focal uncontrolled epilepsy conducted in the Western Infirmary in Glasgow, Scotland [14]. In a large cohort with medically refractory epilepsy, the retention rate for lacosamide was 62% at one year, 45% at two years and 35% at three years [15]. This difference may be explained by the differences in study populations. Novy et al. [15] conducted the study in a tertiary referral center in which each new assessment selects patients who did not respond to a number of previous AEDs (87% to at least six prior AEDs) i.e. the population is becoming increasingly refractory [5] in comparison to our study which was performed in a secondary epilepsy center. Furthermore, in our clinic, lacosamide is often used in the early phase as an adjunctive therapy with a low number of prior AEDs and this improved the possibility of its efficacy and thus higher retention. The discontinuation of the lacosamide has been mainly due to the adverse events (50%) rather than the drug's lack of efficacy (19%). This finding is in line with most of earlier studies [14,16,17] but contrary to Novy et al. [15].

Lamotrigine had the second highest long-term retention rate i.e. 68% which agrees well with the findings in the previous studies (69-74% at 2-3 years) [6,8,18]. Nonetheless, a study executed in a tertiary referral center found a significantly lower retention rate of 40% at three years [19]. Lamotrigine is known to be well tolerated [6,8] and this was the case also in our study.

Levetiracetam had the third highest retention rate at three years (67%). Other studies have reported similar outcomes [8,18,20], but one report found a poorer outcome i.e. a retention rate of 46% at two years [6]. In our study, adverse-events were the cause of discontinuation in only 34% of the cases suggesting that this drug has a favorable tolerability profile.

The retention rate for clobazam was good: 66% of the patients continued the treatment for three years. There are very limited data on the long-term retention rate for clobazam treatment. Indeed, we found only one study (N = 54) which was conducted with highly refractory patients (mean of 8 previous AEDs) reporting a 12 month retention rate (61%) for clobazam [21]. In our audit, clobazam's discontinuation of was equally often due to its adverse effects and its lack of efficacy. According to our results, clobazam can be considered a safe and effective AED. The good long-term retention rate also indicates that the tolerance issues related to adjunctive clobazam treatment might have been overestimated.

Topiramate had a retention rate of 62% following closely behind clobazam. The majority of previous studies have reported significantly lower long-term retention rates between 30-50% for topiramate [6,18,19,22,23]. Perhaps this is attributable to the divergences between the study populations. In our study, as in previous reports, adverse events were the most prominent reason for discontinuation of topiramate treatment out of all of the evaluated eight AEDs. Our results imply that if the patient tolerates the acute toxic effects of topiramate then this is a good indicator of long-term retention, since most withdrawals occur within the first year. This fact has also been mentioned by other investigators [6,18,23].

The retention rate of zonisamide after 36 months as adjunctive therapy in adult patients with refractory focal epilepsy was 60%. One Scandinavian study with a similar patient cohort to ours reported a 12 month retention rate of 54% for zonisamide [24]. Other studies have estimated 45-65% retention rates after 12 months' zonisamide treatment [18,23,26]. One study with a large cohort from a tertiary epilepsy center reported a three year retention rate of 30% [27]. Here, the drug was fairly well tolerated, with only 30% of the subjects discontinuing therapy due to adverse events, in line with an earlier study [24]. In our study, the majority of those patients who discontinued because of tolerability problems, did so during the first 150 days after initiation of zonisamide therapy.

Pregabalin appeared to be one of least well tolerated AEDs in our study with a retention rate of 55%. In recent years, almost all publications with pregabalin have been addressing different indications other than epilepsy. Surprisingly, we found only one report from a tertiary referral center which would have addressed the long-term outcome in a large group of patients. In this study with 402 patients, the estimated 2.5 year retention rate was 32% (26). In their prospective audit, Stephen et al. [28] showed that 50% of those patients treated with pregabalin remained on the drug whereas 46% discontinued the treatment due to adverse events, a similar number as noted here (41%).

Gabapentin was the drug producing the greatest number of complexities leading to discontinuation, with a retention rate of only 40%, a value in line with one earlier report [8]. The data on long-term retention with gabapentin is very limited.

We found that 74% of discontinuations were due to a lack of efficacy and only 11% were attributable to adverse events. Our findings support the impression that gabapentin might be better tolerated than several other AED, but it seems to possess relatively limited efficacy.

Direct comparison of the AEDs is difficult based on the nature of the current study, but it might be worthwhile noting the characteristics of the patients receiving different drugs. The number of patients on each AED was relatively high (over 125 patients) with the exceptions of zonisamide (N = 103) and gabapentin (N = 66). Females and males were equally represented in all of the groups. The known etiology for focal seizures has been considered as a marker of pharmacoresistance [29]. The majority of the patients receiving levetiracetam, lamotrigine and zonisamide had a known etiology. The mean duration of epilepsy varied from 17 years (lacosamide) to 27 years (gabapentin and lamotrigine) highlighting the refractory nature of our patient cohort. The mean doses for all eight AEDs were mostly equal or marginally higher than the World Health Organization (WHO) defined daily doses, suggesting that the overall drug load was not excessive in our patients [30]. Finally, generally is known how much drug resistance is influenced by previous unsatisfactory treatments. As the majority of the patients on lamotrigine, topiramate, pregabalin, zonisamide, clobazam and gabapentin had previously tried a minimum of four AEDs, these cohorts must be characterized as being highly drug resistant. These observations might indicate that patients with a known etiology or/and high number of previous AEDs had more severe epilepsy which could have detrimentally influenced their long-term retention rate. On the other hand, percentage of patients who have previously taken more than 4 AEDs varies from almost 70% with gabapentin, to almost 40% with lacosamide. Incidentally, lacosamide resulted the AED with the best retention rate. This data weaken the observation that lacosamide has a better retention. Overall, no major differences were found with respect to any of the demographical or clinical variables, which allows us to compare these eight AEDs and to hypothesize that differences in their long-term retention rates are drug-related.

A variety of factors may have influenced these retention rates. The mean times to intolerability were in the range of 3.6 (lamotrigine) to 10.2 months (gabapentin). This data might indicate that only a minority of the intolerable adverse events could have been due to rapid titration. Furthermore, if patients terminated treatment with one drug due to adverse events, this was most likely to occur during the first 12 months. This might indicate that if adverse events of an AED do not appear relatively early, they are unlikely to appear after years of treatment as observed in an earlier study [9]. The time to reach a conclusion about insufficient efficacy took somewhat longer, 9 – 13 months with most of the drugs, ranging from only seven months with lacosamide up to 16 months with clobazam.

Some points must be kept in mind when drawing conclusions from this study. All patients were from a single center, which limits external validity of findings. Retrospective nature and the lack of available comparative data are the main disadvantages of retention rate analysis with the current study not being an exception. Furthermore, patients were not randomized to receive any particular AED. Quite likely, physician preference/bias played a role in drug selection and decisions to withdraw certain AED treatments, but no statistical method can remove or fully account this effect [9]. The lack of systematic titration data for AEDs is a limitation of study, as too rapid titration might have an effect on tolerability.

For certain AEDs, the number of patients is relatively small, this is particularly true in the subgroup analysis of elderly patients. Therefore, it might be most appropriate to compare our results with those from other pragmatic studies evaluating retention with adjunctive AEDs in adult patients with refractory focal epilepsy. Even in those cases, the different methodologies and study populations may allow only indirect comparison. However, tolerability has been evaluated analogously in all studies i.e. the percentage of patients terminating drug treatment because of adverse events.

In conclusion, the retention rate appears to be influenced by the sequence in which these AEDs were introduced onto the market. Our study provides important information of many practical aspects of the AED therapy and indicates that there are differences in effectiveness between clobazam, gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin, topiramate and zonisamide as adjunctive treatment for focal refractory epilepsy. Those AEDs that are modestly efficacious but associated with a good tolerability profile might perform better than drugs that are more efficacious with significant tolerability problems. The value of retention rate studies as a valuable information source for physicians is highlighted.

Ethical Standards

This was a non-invasive, retrospective study, which does not oblige ethics committee approval according to Finnish Law on Research. Access to patient records based on decision made by Head of Science Centre, Tampere University Hospital research and innovation services, Science Center.

Conflict of interest and sources of funding statement

Jussi Mäkinen has received support for travel congresses from Biogen-Idec, Boehringer-Ingelheim, Eisai, and Orion Pharma; received speaker honoraria from Boehringer-Ingelheim; received research funding from the Finnish Epilepsy Association and Maire Taponen Foundation; and participated in an advisory board for Eisai.

Jani Raitanen has no conflict of interest.

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Table 1. Demographic and medical characteristics of the patients

	Clobazam	Lamotrigine	Gabapentin	Topiramate	Levetiracetam	Pregabalin	Zonisamide	Lacosamide
Year of introduction onto the Finnish market	1988	1994	1995	1999	2001	2004	2007	2009
Date of full reimbursement	1.1.1990	1.7.1996	1.7.1996	1.9.2000	1.1.2005	1.7.2007	1.11.2008	1.1.2012
N	130	177	66	178	319	127	103	137
Sex								
Female (%)	48.5	55.4	54.5	48.3	49.8	51.2	49.5	51.1
Male (%)	51.5	44.6	45.5	51.7	50.2	48.8	50.5	48.9
Etiology								
Known (%)	29.6	58.7	30.0	34.2	66.5	37.8	56.3	33.5
Unknown (%)	70.4	41.3	70.0	65.8	33.5	62.2	43.7	66.5
Duration of epilepsy (years)								
Mean	20.7	27.1	27.3	23.5	20.2	25.4	23.5	16.6
Range	0-72	1-72	2-63	0-72	0-70	2-70	2-63	0-63
Age								
Mean	44.6	48.1	51.7	49.2	50.6	46.4	42.7	54.0
Range	19-85	19-85	24-85	20-85	19-85	19-85	19-76	21-85

Number of prior AEDs*								
1 (%)	11.8	8.9	4.5	7.9	16.3	7.4	4.9	16.3
2 (%)	15.0	14.8	7.6	14.7	21.5	9.2	7.8	18.8
3 (%)	17.4	17.5	18.2	18.4	20.6	17.6	21.3	25.2
≥ 4 (%)	55.8	58.8	69.7	59.0	41.6	65.8	66.0	39.7

AED = Antiepileptic drug

* = Defined as initiated and withdrawn due to inefficacy

Table 2. Mean duration (months) of treatment and mean dose (mg per day) of AEDs for all patients, patients who discontinued the drug, and for those who continued the treatment

	All patients			Discontinued			On medication			3-year retention rate	
		Duration	Dose		Duration	Dose		Duration	Dose		
	n	Mean (range)	Mean (range)	n	Mean (range)	Mean (range)	n	Mean (range)	Mean (range)	%	95% CI
Levetiracetam	319	23.4 (0-36)	2001 (100-3500)	138	15.5 (0-36)	2271 (250-3500)	181	29.3 (0-36)	1800 (100-3500)	66.7	61.0 to 71.8
Lamotrigine	177	26.1 (0-36)	305 (25-800)	71	16.5 (0-36)	297 (50-800)	106	32.6 (0-36)	310 (25-550)	68.3	60.6 to 74.7
Topiramate	178	24.8 (0-36)	326 (30-1600)	97	19.5 (1-36)	338 (30-1600)	81	31.2 (0-36)	311 (50-600)	61.6	53.8 to 68.5
Pregabalin	127	22.8 (0-36)	415 (25-600)	62	12.1 (0-36)	415 (25-600)	65	33.0 (10-36)	415 (75-600)	54.6	45.4 to 63.0
Zonisamide	103	21.1 (0-36)	354 (25-600)	39	9.9 (0-36)	349 (25-600)	64	27.9 (1-36)	356 (200-600)	60.4	49.5 to 69.6
Clobazam	130	22.4 (0-36)	21.8 (2-200)	50	17.1 (0-36)	23.6 (2-200)	80	25.7 (0-36)	20.7 (5-80)	65.6	55.7 to 73.8
Lacosamide	137	16.9 (0-36)	396 (100-600)	28	7.7 (0-36)	363 (200-600)	109	19.2 (0-36)	405 (100-600)	77.1	67.8 to 84.0
Gabapentin	66	20.8 (1-36)	2692 (900-4800)	55	19.5 (1-36)	2804 (900-4800)	11	27.5 (6-36)	2136 (900-3600)	40.2	28.1 to 52.0

Missing information:

Dose of levetiracetam, 3 patients (discontinued)

Dose of lamotrigine, 4 patients (discontinued)

Dose of topiramate, 2 patients (discontinued)

Dose of pregabalin, 1 patient (discontinued)

Dose of clobazam, 1 patient (discontinued)

Table 3. Reason for discontinuation of one of the tested antiepileptic drug and mean duration (months) of treatment in subjects who discontinued the drug

	Discontinued	Lack of efficacy			Adverse effect			Lack of efficacy and adverse effect			Other reason		
	n	n	%	Duration	n	%	Duration	n	%	Duration	n	%	Duration
Clobazam	38	16	42.1	15.6	14	36.8	5.9	2	5.3	14.6	6	15.8	13.8
Gabapentin	38	28	73.8	12.5	4	10.5	10.2	4	10.5	13.3	2	5.2	2.1
Lacosamide	26	5	19.2	7.3	13	50.0	4.7	2	7.7	6.0	6	23.0	2.9
Lamotrigine	54	29	53.7	12.0	17	31.5	3.6	3	5.6	7.5	5	9.3	12.8
Levetiracetam	100	49	49.0	8.6	34	34.0	5.9	8	8.0	12.4	9	9.0	5.7
Pregabalin	56	22	39.3	8.9	23	41.0	9.0	9	16.1	10.8	2	3.6	17.1
Topiramate	65	16	24.6	12.7	34	52.3	9.1	10	15.4	17.7	5	7.7	9.8
Zonisamide	37	17	46.0	9.6	11	29.7	5.6	7	16.2	8.2	3	8.1	1.0

Table 4. The effect of age and gender on retention rates of the eight antiepileptic drugs

	Three year retention rate					
	Age (years)			Gender		
	< 60	≥ 60	p	Female	Male	p
Clobazam	68.0	73.9	0.57	68.0	70.0	0.98
Gabapentin	43.7	47.7	0.68	45.6	44.4	0.77
Lacosamide	76.7	80.0	0.93	80.6	74.0	0.64
Lamotrigine	67.0	61.4	0.56	66.1	64.6	0.84
Levetiracetam	71.6	74.5	0.67	72.6	72.1	0.98
Pregabalin	53.7	71.9	0.12	53.2	62.2	0.45
Topiramate	61.0	68.6	0.30	69.8	56.3	0.085
Zonisamide	64.8	50.8	0.35	68.2	57.2	0.24

Figure

Figure 1. Retention rates for clobazam, gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin, topiramate, and zonisamide in patients with focal epilepsy by Kaplan-Meier analysis

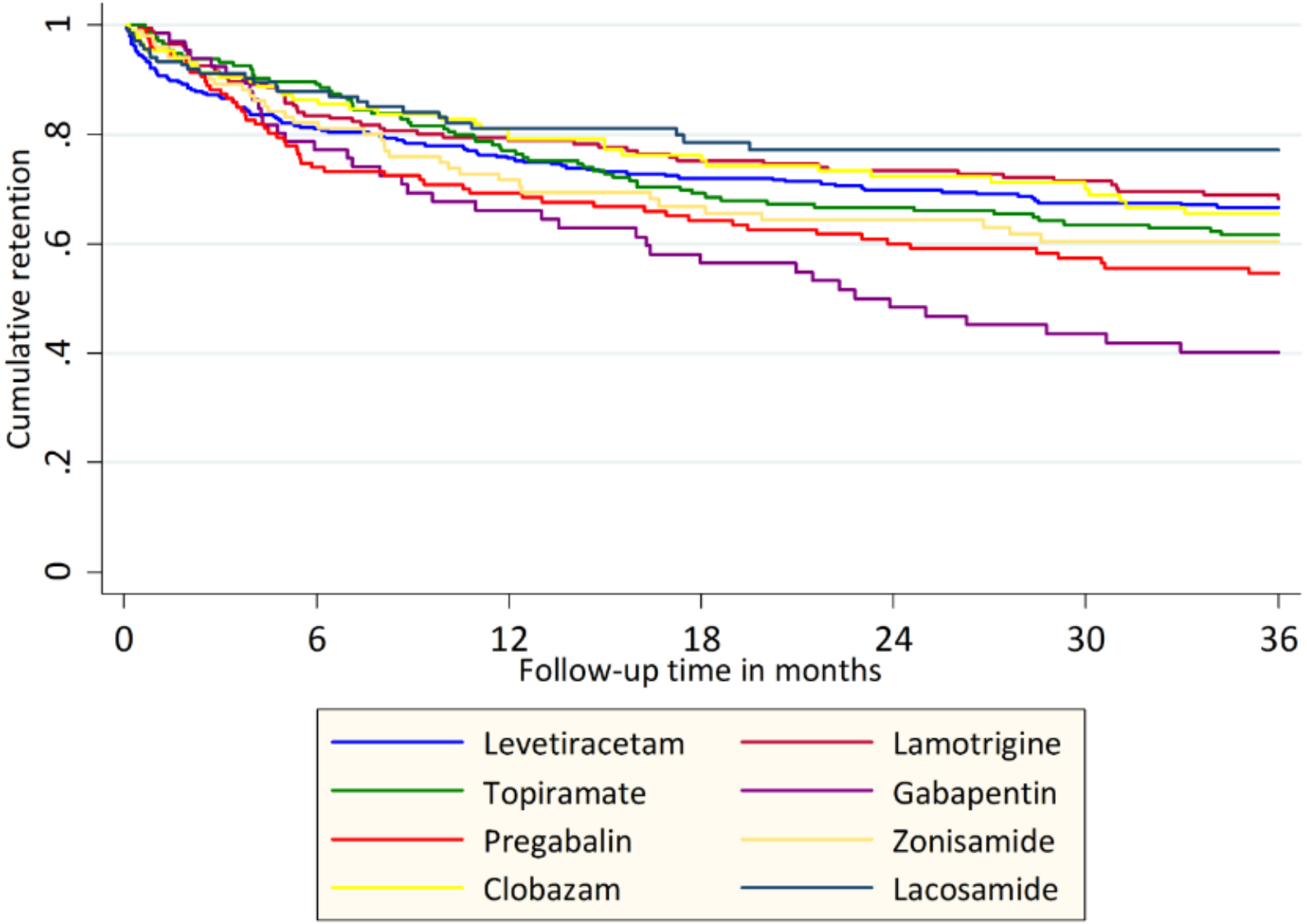

Figure 2. The number of annual initiations (curves, right column) and discontinuations (bars, left column) for antiepileptic drugs used as an adjunctive therapy in focal refractory epilepsy from 2000 to 2014. The location of color code indicates the year of full reimbursement for each antiepileptic drug in Finland