ISSN 1377-7262

K-OPINIONS

building a knowledge network in AEDs

Nr 3 - February 2007

Migraine with aura may induce a seizure, and a seizure can be preceded or followed by a headache, which is often migrainous. Common pathophysiological factors could be responsible for this comorbidity. In monogenic subtypes, a shared genetic susceptibility cannot be excluded.

See p 2-5

Although information on medical conditions is widely available and huge efforts have been made to sensitize the public, prejudices and misunderstandings about epilepsy still remain.`

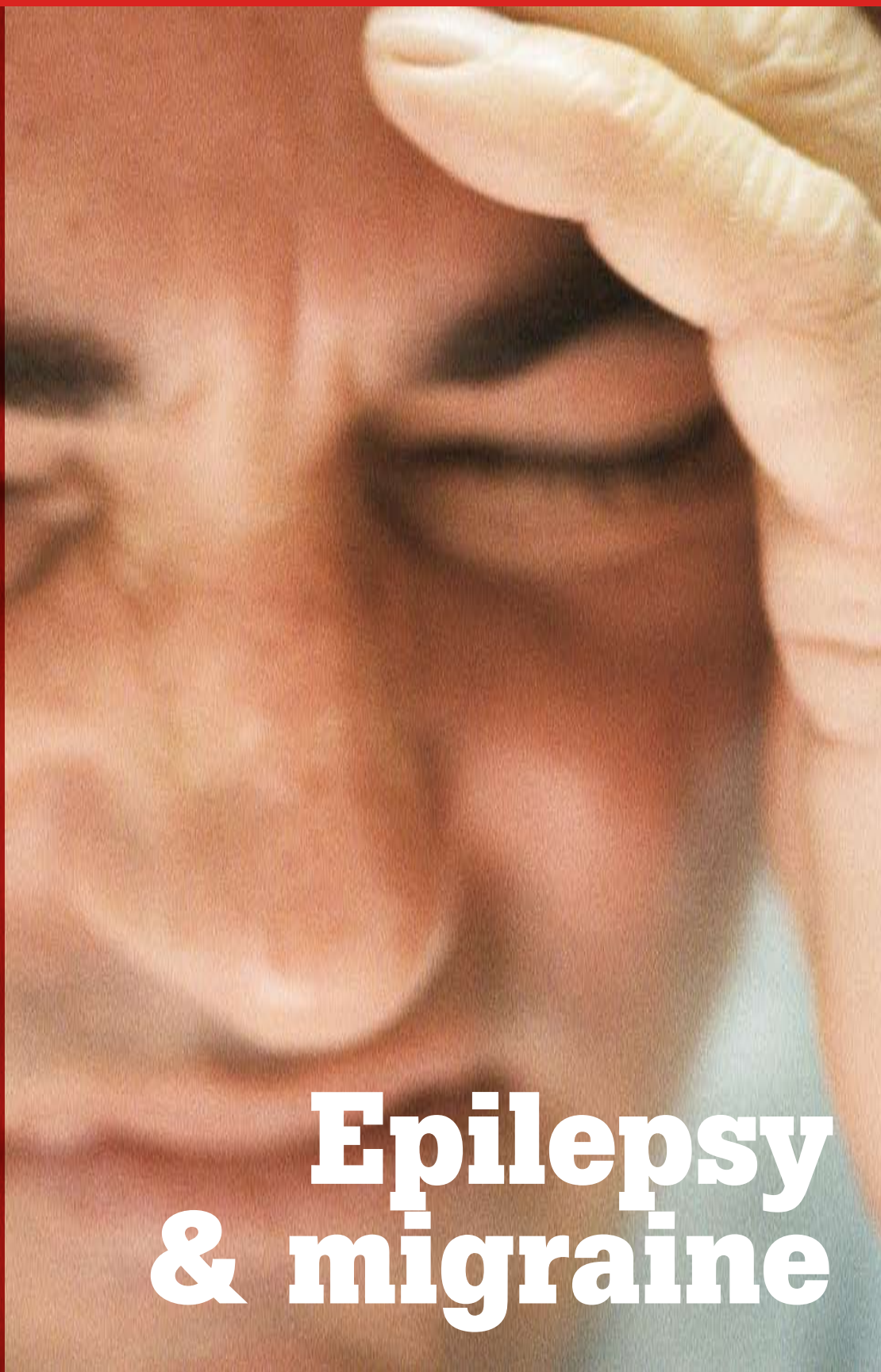
p 6-7

The few clinical studies especially addressing older people show that both seizure control and drug tolerability decrease with advancing age when using standard therapies.

p 8-9

Levetiracetam is the first of the new generation AEDs to demonstrate a non-inferior efficacy and a more favourable tolerability compared to carbamazepine when used as monotherapy in adults with partial onset or generalized tonic-clonic seizures.

p 10-12



Epilepsy & migraine

A review by Jean Schoenen[1,2] and Monica Bolla[1]
Headache Research Unit.
Dept of Neurology[1]
& Res Ctr Cell Mol Neurobiology[2],
Liège University

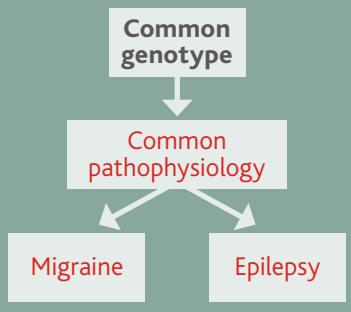
Epilepsy is by far the most frequent disorder comorbid with migraine. The exact causes of the comorbidity are unknown. In most cases, it seems likely that common pathophysiological factors related to cortical dysexcitability and thalamo-cortical rhythms are responsible for the association between the two disorders. In monogenic subtypes, a shared genetic susceptibility cannot be excluded. Although migraine with aura may induce a seizure, much more frequently a seizure can be preceded or followed by a headache which is often migrainous. Such peri-ictal headaches may bias studies on the prevalence of a comorbid association between migraine and epilepsy.

Migraine and epilepsy.
Two of a kind?

Migraine and epilepsy together account for up to 40% of all neurological consultations. On the one hand, almost 18% of females and 6% of males suffer from migraine.[1,2,3] On the other hand, with a prevalence of ± 0.6%, epilepsy is one of the most prevalent neurologic disorders.[4] Despite these high prevalences obscuring the general overview, two decades ago 1992 Andermann and Andermann[5] showed that the prevalence of epilepsy (median 5.9%; range 1-17) in migraineurs greatly exceeds the one found in the general population of 0,5%. Since then a statistically significant association between migraine and epilepsy has been confirmed in several studies.[6]

Migraine and epilepsy share many similarities. Both are genetically-determined chronic paroxysmal disorders characterised by episodic attacks with absent or ill-defined interictal symptoms. The sensory, motor and cognitive characteristics of migraine and epilepsy may overlap. Aura, hallucinations, changes in mood and behaviour or consciousness, and focal sen-

SHARED GENETIC SUSCEPTIBILITY



Some genetic abnormalities, e.g. ATP1A2 mutations, may favour subtypes of migraine such as familial hemiplegic migraine (FHM) and subtypes of seizures.[20,21] FHM and convulsions may also occur as allelic disorders, due to different mutations of the same gene, e.g. on the CACNA1A gene. Moreover, heterozygous mutations in the glutamate transporter EAAT1 gene may also be associated with hemiplegic migraine, seizures and episodic ataxia.[22]

HYPOTHETICAL CO-MORBIDITY MODELS APPLIED TO EPILEPSY & MIGRAINE

Given the phenotypic and especially the genotypic heterogeneity of both disorders, one single explanation for the co-morbidity is unlikely. Albeit, several explanatory hypotheses have been proposed.

Shared genetic abnormalities have been identified in the rare monogenic forms of migraine. However, the common forms of migraine with or without aura, are complex polygenic disorders, as are several of the epileptic syndromes. To explore the *"Common Genetic Risk Factors"* hypothesis, Ottman and Lipton[44] assessed the risk of migraine in relatives of probands (n=1967) with genetic versus non-genetic forms of epilepsy, using two proxy measures of genetic susceptibility: a 1st degree family history of epilepsy and idiopathic/cryptogenic (versus postnatal symptomatic) etiology. Neither of these two measures was associated with risk of migraine in relatives. Furthermore, they also assessed the risk of epilepsy in the relatives of probands with versus without migraine. With the exception of one subgroup (sons of female probands), the risk of epilepsy in relatives was not associated with the proband's history of migraine. Although these results do not rule out that the hypothesis of a shared genetic susceptibility may apply to some subgroups of the disorders, they do not support this model as a global explanation for migraine-epilepsy co-morbidity.

sory or motor symptoms may occur in both conditions. Both disorders may present with headache, as many patients complain of headache before, during and after seizures. Moreover, in some patients, the migraine aura can trigger seizures.[7] Although migraine and epilepsy can independently from each other coexist in one subject, at least six clinical syndromes associating migraine with epilepsy have been described.[8]

Enhanced migraine risk in epileptics

A large epidemiologic survey, based on data of the Epilepsy Family Study of the Columbia University, found a history of migraine in 24% of the epilepsy probands and in 26% of their relatives with epilepsy versus only 15% in relatives without epilepsy.[9] After correction for years at risk and gender, the rate ratio for migraine was 2.4 (95% CI, 2.02 to 2.89) among probands and 2.4 (1.58 to 3.79) among relatives with epilepsy, compared with relatives without epilepsy. Although the migraine risk was highest in probands with epilepsy due to a head trauma, after stratification by seizure type, age at onset, etiology of epilepsy, and history of epilepsy in first-degree relatives, it was significantly higher in every subgroup of probands compared to unaffected relatives. Among probands the age-specific incidence of migraine was increased to a greater extent after onset of epilepsy than before. However, it was also significantly increased in the 5 years prior to onset and even in the years before.

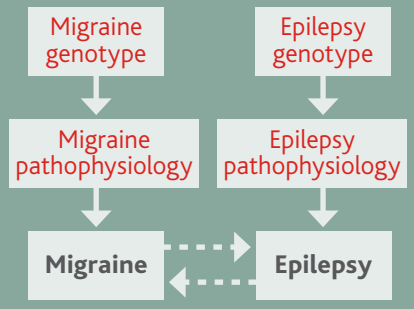
A recent large analysis of data from two Canadian health surveys, evaluating the prevalence of epilepsy and 19 other chronic conditions, concluded that epilepsy patients had a statistically significant higher prevalence of most chronic conditions than the general population.[10] Migraine was found at a prevalence of 185 per 1000 epileptics, twice as frequent as in the general population (RR 2.6, 95% CI 2.2-3.0). When gender was taken into account, migraine was one of 4 most frequent comorbid conditions in females with epilepsy (RR 2.4, 95% CI 2.1-2.7).

Usefulness of comorbidity studies

- **Differential patterns of comorbidity among subtypes of a particular index disorder may unveal the existence of different forms of the condition.**
- **Differential associations between particular pairs of diseases may yield clues regarding the pathogenesis of the index disease.**
- **If two conditions emanate from common underlying etiologic factors, investigations can be targeted to common risk factors.**
- **If the comorbid disorder is caused by the index disease, prevention of the secondary conditions might be possible.**

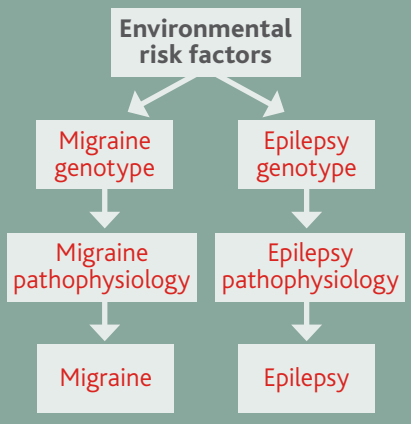
Nevertheless, which conceptual or clinical advantages arise for either disorder from the studies on comorbidity of migraine and epilepsy is not clear yet.

UNIDIRECTIONAL RECIPROCAL INFLUENCE



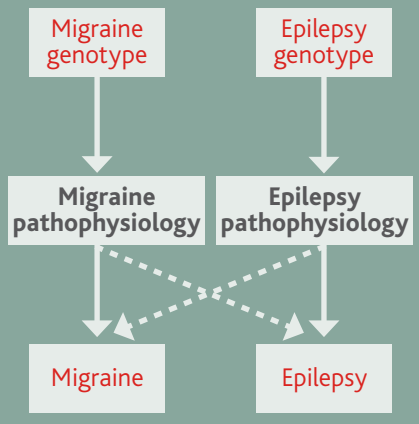
Epilepsy could induce migraine headaches by activating the trigeminovascular system. Conversely, migraine could favour epilepsy by injuring the brain. This could explain the increased incidence of white matter lesions on MRI found in migraine, especially in the subtype with aura.

SHARED ENVIRONMENTAL FACTORS



An example of a shared environmental risk factor explaining the co-morbidity, is head trauma, as it can trigger the appearance of both migraine and epilepsy.

COMMON PATHOPHYSIOLOGICAL FACTOR



Based on certain experimental data and the fact that anticonvulsants are effective in both diseases, e.g. cortical hyperexcitability has been suggested as a common pathophysiologic denominator.[23,24]

The increased risk of stroke and CV disease seen in women suffering from migraine with aura[18] could be attributed to an unidirectional reciprocal influence. But once again, this explanation is unlikely to apply to most patients. It would indeed imply that one disorder should precede the other, whereas in fact, there is an excess risk of migraine both before and after epilepsy onset.[19]

The third model, assuming the existence of *"Shared Environmental Risk Factors"*, cannot account for the increased risk of migraine in subjects with idiopathic or cryptogenic epilepsies.

Finally, the *"Common Pathophysiological Factor"* model is the most attractive. However, in our opinion cortical hyperexcitability is not a satisfactory explanation, as not all AEDs are effective in migraine prevention and as between attacks, the cerebral cortex in migraineurs is characterised by a more complex dysexcitability, chiefly dishabituation, instead of a simple hyperexcitability.[50]

And more epilepsy in (some) migraineurs

The prevalence of epilepsy in people with migraine varies from 1% to 17% (median 5.9%), which is substantially higher than the population prevalence of epilepsy. However, in a recent study of Finnish migraine families only male patients suffering from migraine with aura reported a significant association with stroke and epilepsy (OR 6.76, 95% CI 1.028-44.48), while there was no association with other subtypes of migraine in men or with any subtype in women. In the total population of migraineurs the most frequent associated disorders were hypotension (OR 1.43, 95% CI 1.02-2.01), allergy (OR 1.83, 95% CI 1.34-2.51) and psychiatric disorders (OR 4.09, 95% CI 2.11-7.92).[11]

Comorbidity in childhood

The distinctive features of migraine have been found in several pediatric epilepsy syndromes. These include benign epilepsy of childhood with occipital spike-waves complexes,[12] benign rolandic epilepsy with migraine,[13] mitochondrial encephalomyopathy with lactic acidosis and strokes (MELAS),[14] basilar migraine with seizures and migraine with primary generalized absence epilepsy.[15]

Regarding benign rolandic epilepsy of childhood (BREC), literature data are conflicting. Studies showing an association with migraine[16,17,18] and studies denying it have been published. For instance, Giroud[16] compared the incidence of migraine in four groups of children: 28 children with absence epilepsy, 42 with BREC, 38 with another partial epilepsy and 30 with head trauma. The incidence of migraine in BREC was 62%, compared with 34% in children with absence epilepsy, 8% in those with partial epilepsy, and 6% in those with a history of head trauma. Bladin[20] followed 30 cases of BREC and noted that 20 (67%) patients developed recurrent headaches during the course of the epilepsy and 24 (80%) typical migraine after remission of BREC. An association with migraine has also been reported for other benign partial epilepsies of childhood such as benign occipital epilepsy.[21,22]

All these studies were limited, however, by lack of sensitive diagnostic criteria for childhood migraine. By using revised International Headache Society (ICHD-II) criteria,[23] Wirrell and Hamiwka[24] compared the prevalence of migraine in 3 age- and sex-matched cohorts of 53 children: children with BREC, those with cryptogenic/symptomatic partial epilepsy and those without epilepsy. Children with BREC had higher rates of migraine ($p=0.05$), and of migraine equivalents excluding motion sickness ($p<0.005$) than those without seizures. But as they did not differ significantly from the cryptogenic/symptomatic partial epilepsy cohort, the authors concluded that partial epilepsy, regardless of etiology, is associated with higher rates of migraine in children.

There is also some evidence that children with migraine are more likely to have benign focal epileptiform discharges on their EEG, but these children have no clinical seizures[25,13] and the precise significance of the EEG abnormalities is unknown.

Temporal coincidence of headache and epilepsy

According to the new IHS classification (ICHD-II : code 1.5.5), migraine-triggered seizures, the so-called "migralepsy" (Douglas Davidson)[23] only occur in migraine with aura, either during or within one hour after the aura. As the seizures may overshadow the migraine, the latter is easily overlooked by both patients and physicians. There are also very rare case reports of headache as the sole or most predominant clinical manifestation of an epileptic seizure.[26]

Pre-ictal headaches are relatively rare and short–lived. They occur in ± 10-15% of patients, seem more frequent in focal epilepsies (temporal and occipital) and are usually ipsilateral to the epileptic focus.

Although very common, peri-ictal headaches are also often neglected because of the dramatic neurologic manifestations of the seizures themselves and the frequent inability of the patient to fully observe or recall these headaches.

In a systematic study of the clinical characteristics and lateralizing value of ictal and in particular pre-ictal headache (PIHA) in intractable partial epilepsy, 59% of patients reported recurrent headache and 11% had pre-ictal headache.[27] Among the latter 7% suffered from early PIHA (≤ 30 minutes before seizure onset) and 4% of prodromic PIHA (24 hours to 30 minutes before seizure onset). In all 11 patients with PIHA, the headache was fronto-temporal and fulfilled the diagnostic criteria for migraine without aura in 4 patients (36%) (2 with early PIHA, 2 with prodromic PIHA). Ten patients with PIHA (90%) had temporal lobe epilepsy (TLE) and 8 (72%) had generalized tonic-clonic seizures. Of the 10 patients with TLE and PIHA, 9 suffered from pain ipsilateral to the epileptic focus. All patients with PIHA had a positive family history of migraine. After surgery, the headache disappeared in all 7 patients who became seizure-free and in 1 patient who had a subtotal remission. Only 1 patient with rare seizures continued to have PIHA. The authors hypothesize that vasodilatation and reactive hyperemia at the site of the discharging epileptic focus might be responsible for the ipsilateral migraine-like headache.

In Karaali-Savrun's study[6] pre-ictal headache was present in 20 out of 109 patients (14.81%) with cryptogenic focal and generalized seizures epilepsy. It was localized to the forehead, throbbing in quality, moderate in intensity and significantly more frequent prior to any type of secondary generalized tonic-clonic seizure in comparison to other seizure types.

Similar results were found in another study of intractable partial epilepsy[29]: 47 out of 100 patients (47%) had peri-ictal headache: 11 pre-ictal, 44 post-ictal and 8 both pre- and post-ictal headache. In 90% of patients (27/30) with temporal lobe epilespy (TLE) the peri-ictal headache was ipsilateral to the seizure focus while in extratemporal epilepsy (ETE) only 2 out of 17 patients (12%) had ipsilateral headaches ($p<0.001$). The peri-ictal headaches had the characteristics of migraine without aura in 18 of 30 (60%) patients with TLE and in 7 of 17 (41%) of those with ETE ($p=0,24$). However, in another study[30] migraine-like peri-ictal headache was also ipsilateral in patients with a seizure focus in the occipital lobe.

A comparable overall incidence of seizure-associated headaches was found in a study of 110 outpatients from an epilepsy referral center.[31] Forty-seven (43%) reported headache associated with their seizures, 43 exclusively post-ictal headaches, but only 1 exclusively pre-ictal headaches. Three patients had both

pre- and post-ictal headaches. In the majority of patients, post-ictal headaches occurred in more than 50% of the seizures. Post-ictal headaches were associated with focal seizures in 23 patients and/or with generalized seizures in 54 patients. According to IHS criteria, the headaches were classified as migraine-like in 34% of patients and as tension-type headache in 34% of patients; they could not be classified in 21% of patients. There was no relationship between the localization of the epileptogenic focus, localization of the headache, or the headache classification.

Possible mechanisms of the migraine-epilepsy interactions

Except for seizures triggered by a migraine aura, the mechanisms underlying seizure-related pre-ictal headaches are poorly understood. One may speculate that a thalamocortical dysrhythmia preceding the seizure onset, or endogenous/environmental factors able to trigger a seizure (e.g. stress or exteroceptive stimuli) may favour headache. It is noteworthy that primary headaches such as migraine and tension-type headache are more prevalent in the perimenstrual period in epileptic women with menstrually-related seizures.

Concerning post-ictal headaches, there are good reasons to believe that these are due to an activation of the trigeminovascular system, which is the major pain-signalling system of the viscera brain. This probably explains why most of these headaches have migrainous features and why they may overlie the epileptic focus. In patients who report post-ictal tension-type like headaches, strain in neck muscles during the seizure may play a pathogenic role. Unfortunately, post-ictal headaches are undertreated, as for instance information on the therapeutic effectiveness of migraine-specific drugs such as triptans, is lacking.

Other pathophysiological factors involved in migraine may be relevant: for instance, several lines of evidence, coming from morphological, biochemical, imaging and genetic studies, suggest that at least some subtypes of migraine may be related to a mitochondrial defect.[33] This might explain why enhancers of mitochondrial metabolism, such as riboflavin and co-enzyme Q, are effective in migraine prevention.[34,35] Impaired mitochondrial energy mechanisms may favour seizure activity by various molecular mechanisms and mitochondrial cytopathies may classically express themselves phenotypically as a combination of migraine with aura, epilepsy and strokes.[36,37] Interestingly, in Ottman & Lipton's study[44] sons of migrainous female probands had an increased risk of epilepsy which might be related to maternal transmission of a mitochondrial defect.

Abnormalities of scalp-recorded high frequency oscillations in evoked cortical potentials have been found in migraine between attacks.[38] These oscillations reflect activity in thalamocortical circuits, which are also involved in the pathogenesis of seizures. Thalamo-cortical dysrhythmia could thus be a common phenomenon to both disorders.

Implications for therapy

If migraine and epilepsy are comorbid in a patient, an anticonvulsant effective in migraine prevention should be preferred. As anticonvulsants are generally less well tolerated in migraineurs than in epileptics, a slow dose escalation is mandatory in migraine, as is the search for the lowest efficacious dose.

While the classical anti-epileptic drugs such as phenobarbital, phenytoin or carbamazepine, have no prophylactic effect in migraine, valproic acid and topiramate surely have (grade I evidence). Up to now, there is only circumstancial evidence suggesting efficacy for gabapentin, levetiracetam, tiagabide and zonisamide. Lamotrigine, one of the most effective strategies for the prevention of migraine with aura[39,40], lacks efficacy in migraine without aura[41], which represents 80% of all migraines. This observation on its own indicates that explaining the migraine-epilepsy comorbidity by cortical hyperexcitability is not reasonable.

Finally, adequate treatment for postictal headaches should be provided in epileptic patients. One should not refrain from using triptans, if the headaches are migrainous.

Further studies are clearly needed to better understand the genetic, pathophysiologic and therapeutic interplay between migraine and epilepsy.

References: see page 8

Comorbid migraine appears to worsen the prognosis of epilepsy

Of the few studies addressing the prognosis of migraine and epilepsy in co-morbid patients, the publication by Velioglu[32] provides the most informative and reliable results. Two matched cohorts of epileptic patients, one with epilepsy-migraine comorbidity (n=59), the other with only epilepsy (n=56), were prospectively followed for 5-10 year. The epilepsy-migraine group had a significantly lower cumulative probability of being seizure-free (46%) over 10 years, compared to the epilepsy only group (12%). Moreover, the epilepsy-migraine group had a significantly longer duration of epilepsy, a lower early treatment response, a higher incidence of intractable epilepsy, a higher need for polytherapy to achieve remission, and more problems for seizure control and medication for at least the last 2 years of follow-up.

Post-ictal headaches are more prevalent (from 23.8% to 48%) and may last for several hours. Post-ictal headache is migraine-like in 25.9% to 69% and occurs more frequently in patients with a positive history of migraine.[28] It can be disabling and affect the patient's quality of life. It is generally undertreated.[31]

Post-ictal headache occurs more often after secondary generalized tonic-clonic seizures, in which case it usually lacks migrainous characteristics. Although partial epilepsies are less associated with post-ictal headache, the latter are more often migraine-like and ipsilateral to the epilleptic focus, especially in occipital lobe epilepsy.[30]

In spite of efforts and achievements.
Epilepsy: an inconvenient true.

In the past decades enormous progress has been made in the diagnosis and especially the therapy of epilepsy. Valuable campaigns to inform and sensitize the population about epilepsy have been launched. Today, information on medical conditions is available to all on a scale never seen before... So what went wrong, as questions, prejudices and misunderstandings about epilepsy still remain?

Paul Bourgois, MD
Department of Neurology,
AZ Groeninghe, Kortrijk

As many still think about epilepsy as a necessarily handicapping, hardly treatable and even uncurable disease, patients as well as their families experience epilepsy as a stigma, starting from the diagnosis on. Confronted with such misconceptions, patients refrain from outing themselves as "epileptics". Another reason making epilepsy a "hidden" disease, is the advent of highly effective anti-epileptics. Years ago, seizures were not that rare. Today, only few people have ever witnessed a full clonic-tonic seizure followed by unconsciousness, as most patients remain seizure-free for most of the time.

As a consequence, a patient having a seizure in public, is stared at by a horrified crowd. Even before the patient can take notice, he is hurried away by ambulance towards the emergency department of the nearby hospital. This explains why in Belgium, neurologists see a lot of reluctant epilepsy patients, who don't really want, neither need specialised help, as for patients with occasional seizures under treatment, a hospitalization is seldom mandatory.

Echeloned care is a fact

An epilepsy patient spontaneously seeking specialised help, is rather uncommon. Even when confronted with partners or parents who witnessed the seizure, they often tend to minimize the extent of it or even deny it completely. The normal caregiving pathway begins at the GP, who usually suspects the diagnosis of epilepsy based on clinical signs only. The diagnosis will then be evidenced and documented by the second line neurologist by means of advanced medical imaging, EEG... For a first seizure, hospitalization eventually makes sense to fine-tune the diagnosis and start an adequate treatment. The last decade, medication became more and more

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a specialist's task, as most GPs do not feel very comfortable with the abundance of new antiepileptic drugs available today. Once stabilized under therapy, the patient's follow-up is assumed by his GP, as a once-a-year check by the neurologist is generally sufficient.

Finally, second line neurologists refer some patients with diagnostic problems or unresponsive to standard treatments (and occasionally patients who want a second opinion) to the next level. It is obvious for third line centres to dispose of more sophisticated diagnostic tools such as video monitoring of seizures, PET-scan... and highly specialised therapeutic techniques, e.g. vagal nerve stimulation or neurosurgery. Nowadays, institutionalisation is restricted to the rare cases needing adjusted care because of extremely therapy resistance and/or concomitant mental retardation.

Echeloned information is still a challenge

So the good news is that we dispose of skilled GPs and specialists, well-equiped centres, efficacious medications and streamlined caregiving pathways, respecting everyone's role and competences. But although we are living in the so-called "information era", ignorance about this disease still rules. Today's patients indeed can surf on the word wide web, but internet is not always a very reliable source. Moreover, as epilepsy has many faces, patients easily go astray in the overwhelming bulk of information available. Based on our own experience with a brochure we made for our Stroke Unit patients, we think that in this respect an objective and concise booklet could be of great help.

To avoid the unnecessary burden on the emergency department every time someone has a seizure in public, at the population level, epilepsy should no longer be a taboo. Once epilepsy has become accepted, patients will be less reluctant to out themselves as epileptics. Nowadays, some patients deliberately ignore the ban on driving, endangering their own and others' lives, just because they can't bear the idea that someone could ask them for an explanation why all of a sudden they no longer have a driving license.

At the level of the patient's immediate entourage, including colleagues at work or teachers at school, precise information explaining the do's and don'ts in case of a seizure, should be available.

And finally, for the patients themselves and their family, a generic list of topics is mandatory, as our experience shows that each time we see a newly diagnosed patient, the same questions about prognosis, therapeutic possibilities, school performances, job opportunities... arise.

CALL FOR WITNESSES

A clear and detailed description of the seizure can be crucial for assessing the seizure type and can even reveal important clues for localizing a focus. In the past, it was proven to be useful asking parents to record their convulsing children on video.

An even better approach would be to "professionalize" the entourage at a point they can recognize diagnostic relevant features.

In our Neurology Department we assessed the feasibility of such approach starting with our own in-house nursing staff. To sharpen the awareness of the paramedics for diagnostic clues, while coping with seizures, we developed a tailor-made course. The didactic qualities of this new learning tool where evaluated by asking the nurses to describe three different seizure types recorded on a DVD, before and after completion of their course.

It was just astonishing to notice how much more details were notified: the coloration of the skin, the deviation of the eyes, the extent of the myoclonies, the duration of the unconsciousness, the presence of urinary incontinence...

In a next step, the acquired skills were implemented in daily practice. By means of a custom form the observations during a seizure are recorded in a standardized way. This allows the attending neurologist to make a more precise evaluation of the type and extend of the seizure.

Encouraged by the enthusiastic and convincing experiences within our own department, now other departments also tend to adopt the same procedure.

SELF-HELP IS UNDERWAY

As a professionally assisted patients organization, among other tasks, the *Vlaamse Liga tegen Epilepsie/Ligue francophone belge contre l'épilepsie* provides epilepsy patients and their families with specific information about social problems encountered by patients with epilepsy (insurance, family, school, job...). For information seekers, a glance at their site is recommended: *http://www.ligueepilepsie.be/fr/*

http://www.epilepsieliga.be/files/info/home.php

Assignments for first line caregivers

- Inform and above all, counsel family members
- Check compliance
  - phenytoin, carbamazepin and valproate blood levels can be determined
  - emphasize the importance of sleeping times and alcohol withdrawal
  - make sure a patient respects a car driving ban
- Look forward
  - screen for medication side effects
  - ask proactively about behaviour and achievements at school/work
  - warn patients for possible pharmacological interactions
  - discuss (anti)conception before the patient is pregnant

60th Annual Meeting of the American Epilepsy Society, San Diego, 01-05 December 2006

Although new onset epilepsy in the elderly is far from uncommon, only few clinical studies especially addressing elderly people are carried out. Nonetheless, using established standard therapies, both seizure control and drug tolerability decrease with advancing age.

AEDs in elderly people.

Age inversely correlated to efficacy and tolerability.

In the Veterans Affairs Cooperative Study[1], a randomized, double-blind, double dummy, parallel study, 593 older individuals, on average 72 years old, with newly diagnosed seizures were assigned to standard therapy with carbamazepine, gabapentin or lamotrigine. With respect to seizure control at 12 months, the overall results showed little difference among groups.

But what is more interesting, when dividing the study population into three age groups, the intent to treat seizure free rate at 12 months showed a steady decline from the youngest to the oldest group for all three treatments.[2] (See Table)

Irrespective of the AED used, seizure free rates are declining with age

	60-69 yrs	70-79 yrs	80+ yrs
carbamazepine	27.6	21.4	17.1
gabapentin	20.3	27.8	17.1
lamotrigine	32.9	27.1	20.7

As could be expected, due to their superior tolerability, the patients randomized to the newer AEDs gabapentin and lamotrigine demonstrated a significantly better one-year retention versus carbamazepine (difference in termination for adverse events p=0.0001). However, sedation, which was an important side effect in this study population, showed a steady increase in age-related incidence also for the lamotrigine and gabapentin groups. In particular, two-thirds (65.6%) of the gabapentin 80+ group reported sedation, compared with just over half that number (34.4%) for the 60-69 group.

Risk for drug-drug interactions underestimated

Another problem often encountered in the elderly is the risk for interactions with concomitant medication. A retrospective cohort study in epilepsy patients based on a US claims database (2001-2004) confirmed that elderly people taking AEDs are at increased risk for

exposure to medications that may incur a potentially adverse pharmacokinetic interaction.[3] (See Table)

As expected, the risk of addition of concomitant medication at some time after an AED is initiated, is inversely related to the patient's general health condition. However, independently from co-morbidities, the risk of drug-drug interactions shows significantly higher in females and also increases with advancing age. These real life findings emphasize the importance of avoiding enzyme inducing antiepileptic drugs, especially in aging, female patients, irrespectively of their general health condition.

Hazard ratio of first addition of medication possibly causing pharmacological interactions in elderly epilepsy patients

Covariates	HR [95% CI]
Male (vs female)	0.8 [0.772;0.828]
Age	
18-34 (vs 0-17)	1.112 [1.059;1.169]
35-54 (vs 0-17)	1.379 [1.317;1.443]
55-64 (vs 0-17)	1.636 [1.532;1.746]
65+ (vs 0-17)	1.749 [1.574;1.944]
General health condition	
mildly affected (vs good)	1.434 [1.361;1.512]
severely affected (vs good)	1.536 [1.450;1.629]

All p-values <0.001

Levetiracetam is efficacious, well tolerated...

The above mentioned problems arising in older epilepsy patients explain the interest in novel, well tolerated AEDs such as levetiracetam. A first study of which the results were presented, was an open label trial evaluating the efficacy and safety of low dosed levetiracetam as monotherapy in elderly patients with cryptogenic epilepsy.[4] New onset epilepsy in older people is often cryptogenic as the seizures occur without a defined provoking factor or without an obvious remote or current neurological pathology.

Fourteen patients > 60 years old (mean age 68 years), newly diagnosed for cryptogenic epilepsy and having experienced at least 2 seizures, were enrolled. Starting at 250 mg/day, levetiracetam was uptitrated by 250 mg a week. Every 3 months all patients performed a visit to access efficacy and safety through neurological examination, seizure diary, EEG, complete blood test, MMSE, SF12, NPI...

All patients completed the study. After a follow-up of 12 months, they all became seizure free: 8 patients at 1000 mg/day and 6 patients who needed a higher dose (up to 2000 mg/day) for seizure control. Levetiracetam also proved to be well tolerated without any interaction with other concomitant treatments. Most often encountered adverse effects were somnolence, dizziness, headache, agitation and irritability, all mild and limited in time. Moreover, after levetiracetam treatment, all patients showed an improvement in quality of life as their level of autonomy and relationships increased.

... and improves QoL in the elderly

The efficacy and the superior tolerability of levetiracetam in elderly epileptic patients were confirmed in a second study with carbamazepine as a comparator.[5] Indeed, the retention in the study was significantly higher for levetiracetam than for carbamazepine. The efficacy of both study drugs showed similar, but carbamazepine caused significantly more side effects, resulting in earlier termination of treatment.

In this trial, 24 consecutive, newly diagnosed outpatients who experienced at least two unprovoked seizures in the past 12 months were randomized to monotherapy with 1000 mg levetiracetam/day or 600 mg carbamazepine/day. Nine out of 24 patients (6 in the levetiracetam group and 3 in the carbamazepine group), showed minimal EEG abnormalities at basal evaluation consisting of focal theta waves, that disappeared after 12 weeks of treatment in all patients.

All patients but 3 (2 on carbamazepine and 1 on levetiracetam) became seizure-free for 48 weeks of follow up. In the non-responders, the

dosage was subsequently increased to respectively 800 mg and 1500 mg a day. All levetiracetam treated patients completed the follow up period remaining on the original drug, achieving a 100% retention rate. On the other hand, 3 patients on carbamazepine discontinued their therapy for side effects (2 patients with marked somnolence and one patient with dizziness). These results also suggest that the optimal dose of both drugs may be lower in elderly compared with the general epileptic population.

Once again an impressive difference in the impact of drug on quality of life was noticed. The SF-36, administered at baseline and throughout the study, showed a poor impact of treatment on quality of life in all levetiracetam patients, while 4 out of 12 carbamazepine patients showed a worsening in several items of the questionnaire.

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3 French J, Grossman P, Gidal B, Le Teuff G, Bugli C. Potential Drug Interactions in Epilepsy Patients: Risk of Concomitant Medication Use. Poster Number: 2.223
4 Barbato G, Alfieri P, Arlomede R, Visco G, Terracciano AM. Elderly Patients with Cryptogenic Epilepsy Treated with Levetiracetam as Monotherapy. Poster Number: 2.104
5 Paciello N, Marchi PN, Chiummiento M,Mazza S, Paciello M. Levetiracetam vs Carbamazepine in Epileptic Elderly Patients. Poster Number: 2.144

Levetiracetam is the first of the new generation antiepileptic drugs to demonstrate a non-inferior efficacy to carbamazepine when used as monotherapy in adult patients with partial onset or generalized tonic-clonic seizures and to show a significantly more favourable tolerability profile in a head-to-head study that used a rigorous non-inferiority design and an optimal use of the comparator.

B. Sadzot
Dept of Neurology, Epilepsy Unit,
CHU Liège, Belgium

Benefits from levetiracetam as starter therapy in epilepsy.

As more than 50% of patients with newly diagnosed epilepsy will achieve adequate seizure control with only one antieplipetic drug, monotherapy is the treatment strategy of choice. For patients with partial epilepsy or generalized tonic-clonic seizures carbamazepine is a first-line standard drug. Patients with generalized or multiple seizure types and patients without a clearly determined type of seizure or epilepsy syndrome at the time of treatment initiation are mostly treated with valproic acid.

These older medications are certainly useful. But as they are not devoid of potentially hazardous side effects, in particular their propensity to cause neurotoxicity, alternative treatment options are more than welcome. Ideally, the new generation antiepileptics will allow us to deal with possible drug-drug interactions and contraindications, to obtain a quicker onset of action or to adopt easier titration schedules.

A potent broadspectrum antiepileptic

In the studies published up to now, levetiracetam appears as a potent antiepileptic, controlling a broad range of seizure types. Moreover, it is devoid of the drug-drug interaction seen with older AEDs and it can rapidly be uptitrated to therapeutic doses. In the mean time it has also proven its efficacy and safety in so-called "special populations" such as in the elderly[1], and it offers a therapeutic option in young women at childbearing age, as it does not interact with hormonal anticonceptives. Preliminary data that still need confirmation on a larger scale even suggest that it might be devoid of teratogenic effects.[2]

In the past, levetiracetam has already proven its efficacy as add-on therapy in adults as well as in children with partial and generalized seizures.[3] Levetiracetam has also been evaluated as initial monotherapy. This was done in 82 children and adolescents with newly onset epilepsy (excluding absences) at a mean dose of 21.8 mg/kg/day.[4] A retrospective review of their medical records revealed that 85.4% of these patients achieved at least 6-month seizure freedom. In this study only 4 patients discontinued their study drug due to levetiracetam imputable adverse events.[5]

Established efficacy as first choice

Up to now, levetiracetam has been registered as an adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy and as adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy. But based on the results of a well-conducted comparative monotherapy study in patients with newly or recently diagnosed epilepsy and suffering from partial or generalized tonic-clonic seizures (Study N01061)[6], the current indication will be extended to monotherapy treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

The LEV N1061 study is a randomized, double-blind, head-to-head comparison study with carbamazepine-CR, the reference drug, held in adult patients with newly diagnosed partial, or generalized tonic-clonic epilepsy (exclud-

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ing idiopathic generalized epilepsy). The 576 randomized patients were assigned to levetiracetam 1 000 mg/day or carbamazepine CR 400 mg/day. This dose was maintained for a six-month evaluation period or until the next seizure. When a seizure occurred, doses were increased to levetiracetam 2 000 mg/day and carbamazepine CR 800 mg/day or levetiracetam 3 000 mg/day and carbamazepine CR 1 200 mg/day. Once six-month seizure freedom was achieved, patients entered a six-month maintenance period.

Better tolerated

In this trial levetiracetam demonstrated six- and 12-month seizure freedom rates of 73.0% and 56.6% respectively, when used as monotherapy in newly diagnosed patients, providing evidence that levetiracetam is as effective as carbamazepine-CR as first-line therapy for patients with partial or generalized tonic-clonic seizures. Moreover, levetiracetam was better tolerated than carbamazepine-CR as fewer patients receiving levetiracetam had adverse events leading to drug discontinuation or dose change (16.1% versus 23.0%, p=0.046).

A study demonstrating efficacy and tolerability.

Levetiracetam as a first choice AED.

The pivotal comparative monotherapy study N01061 is a Phase III, multicentre, double-blind, randomized non-inferiority study evaluating the efficacy and the tolerability of levetiracetam in monotherapy, with carbamazepine as an active comparator, in newly diagnosed epilepsy with partial or generalized tonic-clonic seizures.*

The primary objective was to prove that monotherapy treatment with levetiracetam 1 000 to 3 000 mg/day is non-inferior to monotherapy with CBZ 400 to 1 200 mg/day in achieving 6-month seizure freedom in adults (≥ 16 years old) with newly or recently diagnosed epilepsy, suffering from partial or generalized tonic-clonic seizures. The secondary objective was to compare the safety and tolerability of both drugs.

A total of 579 subjects with newly or recently diagnosed epilepsy having experienced at least 2 unprovoked seizures separated by a minimum of 48 hours in the year preceding randomization, of which at least 1 seizure occurred in the last 3 months, were elegible for the study. They were randomized to receive either levetiracetam (n = 288) or controlled release carbamazepine (n = 291) as a comparator. The ITT population totalled 576 patiens, 285 in the levetiracetam group and 291 in the carbamazepine group.

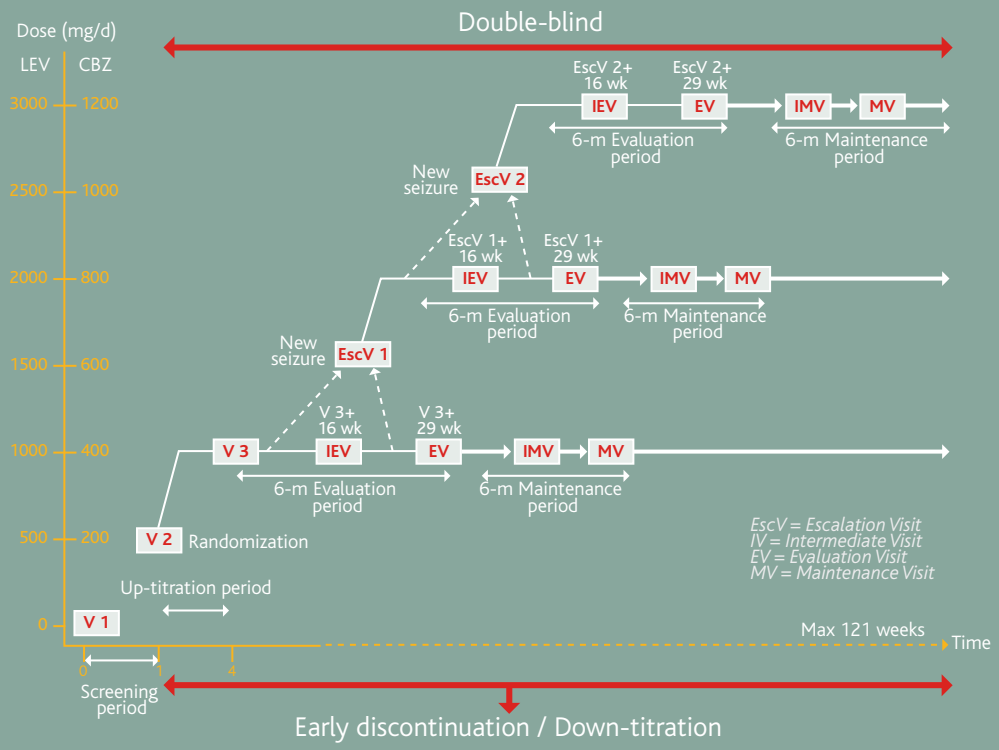
The study consisted of several periods. After an initial 1-week screening period, the therapy was uptitrated during 2 weeks, followed by a 1-week stabilization period. Patients then started a regimen of carbamazepine CR 400 mg/day or levetiracetam 1 000 mg/day and entered an evaluation period of 6 months.

If a seizure occurred during this 6-month evaluation period, a 2-week dose escalation period to the second target daily dose (carbamazepine CR 2 x 400 mg/day or levetiracetam 2 x 1 000 mg/day) was scheduled. After a 1-week stabilization period at the new dose, the patients once again entered a 26-week evaluation period.

The patients experiencing a new seizure during this second evaluation period were further uptitrated to the third target daily dose (carbamazepine CR 3 x 400 mg/day or levetiracetam 3 x 1 000 mg/day). Whatever dose was needed to control their seizures, all patients were observed during a maintenance period of 26 weeks, starting one week after the point of time the last efficacious dose was started.

** The EMEA's Committee for Proprietary Medicinal Products (CPMP), advises that therapeutic confirmatory monotherapy studies in newly or recently diagnosed patients should always be randomized, double-blind positive controlled trials aiming to demonstrate at least a similar benefit/risk balance of a test product as compared to an acknowledged standard product at its optimal use.*

STUDY N1061 DESIGN



For each subject, the 6-month observation period was defined as starting at the latest of the three following dates: Visit 3, or Escalation Visit 1 + 21 days or Escalation Visit 2 + 21 days. The end date of the 6-month seizure-freedom evaluation period was equal to the start date + 181 days, so that the number of evaluated days was 182.

K-OPINIONS

So, for an individual subject the maximum duration of the study was 121 weeks. All patients dropping out of the evaluation period were presumed not having achieved a 6-month seizure freedom and were consequently counted as non-seizure free.

Convincing outcomes

The primary efficacy variable was the proportion of the per-protocol subjects with 6-month seizure freedom at the last evaluated dose. Of the 472 patients who adhered to the treatment protocol, 73.0% of levetiracetam and 72.8% of carbamazepine-CR patients were seizure-free for six months.

Amongst the patients who completed the maintenance phase of the study, 56.6% of those in the levetiracetam group and 58.5% in the carbamazepine CR-group were seizure-free for 12 months.

It is noteworthy that significantly fewer patients on levetiracetam needed to stop treatment or change their dose because of an adverse event than those taking carbamazepine CR (16.1% versus 23.0%; p=0.046).

ONGOING LEVETRIRACETAM STUDIES IN NEWLY DIAGNOSED EPILEPSY

At the end of this study the patients who continued the study drug, had three options for continuing:

Switch to a double-blind levetiracetam/carbamazpine extension study

1) Study N01093, a double-blind long-term follow-up study in which subjects who benefited from their randomized treatment are able to continue their study drug. The aim is to evaluate the long-term safety of levetiracetam and carbamazepine in monotherapy.

Conversion (2 to 6 weeks) to open label levetiracetam

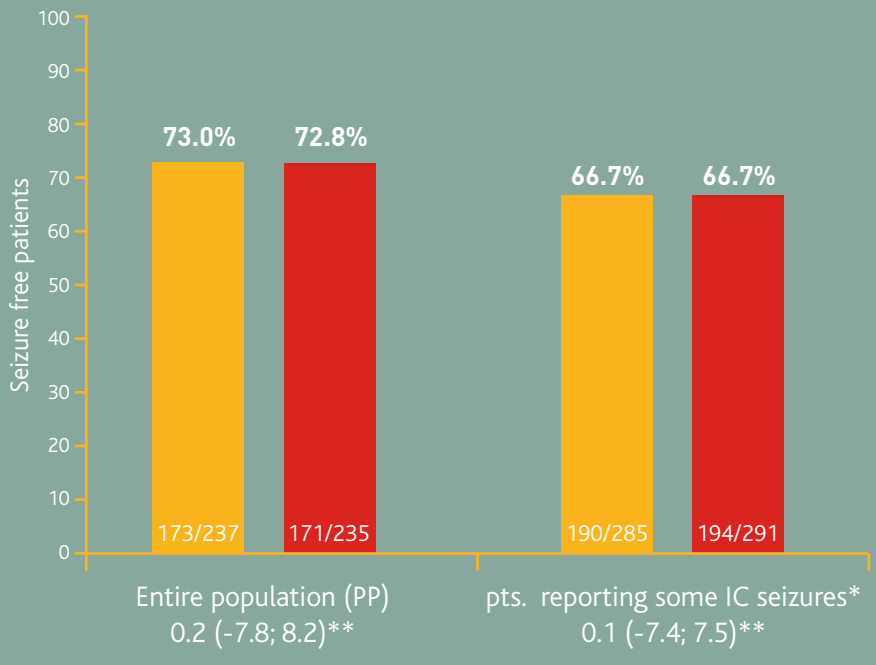
2) Study N01127, intended to allow subjects from N01061 or N01093 to continue to receive levetiracetam (including subjects previously exposed to carbamazepine who switched to levetiracetam). The aim is to evaluate the long-term (around 4 years) safety of levetiracetam as per adverse events reporting.

3) Study N01091, an open label Named Patient program

One additional study is ongoing, N01175, a phase IIIb therapeutic confirmatory, open-label, multicentre, randomized, community-based trial investigating the efficacy and safety of levetiracetam compared to valproic acid and carbamazepine as monotherapy in subjects with newly diagnosed epilepsy.

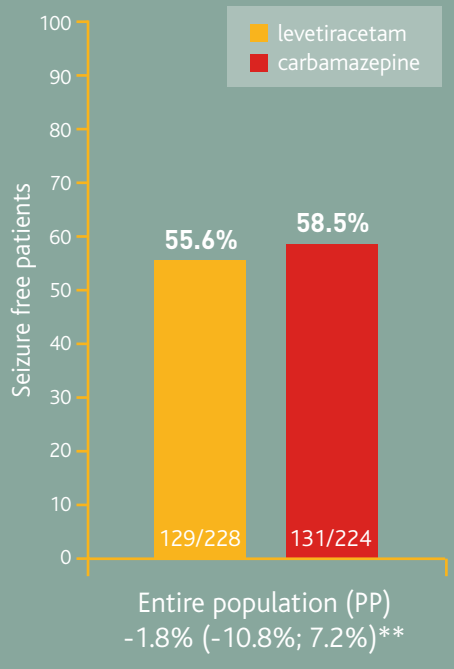
SIX-MONTH SEIZURE FREEDOM

entire PP- population (pimary endpoint)
and in the subset of patients reporting partial seizures



ONE-YEAR SEIZURE FREEDOM

entire PP-population (secundary endpoint)



** Within the ITT population, it was possible to identify those reporting partial seizures Type IC (partial onset seizures with secondary generalisation).*
*** Adjusted Difference (LEV-CBZ) 95%CI*

An edition of Systole, Place de l'Alma 3, 1200 Brussels
Editors: W. Eerlings, M. Cooreman; Responsible editor: C. Chatelle

Made possible by an educational grant of

THE UCB INSTITUTE OF EPILEPSY
www.ucb-ioe.be