Seizure 23 (2014) 585–591

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Review

New antiepileptic drugs and women

Arne Reimers [a,b,*]

[a] Department of Clinical Pharmacology, St. Olavs University Hospital, Trondheim, Norway
[b] Department of Laboratory Medicine, Children's and Women's Health, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

ARTICLE INFO

Article history:
Received 21 March 2014
Received in revised form 8 May 2014
Accepted 10 May 2014

Keywords:
New antiepileptic drugs
Women
Contraception
Pregnancy
Breastfeeding
Menopause

ABSTRACT

Since 1990, sixteen new antiepileptic drugs (AEDs) have been introduced. Most of these new AEDs have only been insufficiently studied with respect to women-specific aspects such as endogenous sex hormones, hormonal contraception, pregnancy, breastfeeding, or menopause. This is of concern because it has been shown for some of the new AEDs that these factors may have a clinically significant impact on their pharmacokinetics and seizure control. Also, new AEDs may affect hormone homeostasis and pass over into breast milk. The best studied of the new AEDs are lamotrigine, levetiracetam and oxcarbazepine. Although gabapentin and pregabalin are even more frequently used (due to their therapeutic effects in nonepileptic conditions), our understanding of these two drugs in relation to women's issues is surprisingly poor. Little to nothing is known about zonisamide, retigabine/ezogabine, lacosamide, perampanel and the other new AEDs. Nevertheless, many small studies and case series have been published on new AEDs and women-specific aspects. This review gives an overview on what is known today.

1. Introduction

Antiepileptic drugs (AEDs) are widely used. They are prescribed as standard treatment not only for epilepsies, but for a variety of nonepileptic conditions as well, mainly bipolar spectrum disorders and chronic pain states.[1,2] In fact, only one out of three AED users takes these drugs for epilepsy.[3,4] A large number of AEDs are available. Since 1990, 16 new (or "second-generation") AEDs have been registered: lamotrigine, vigabatrin, tiagabine, felbamate, topiramate, gabapentin, pregabalin, levetiracetam, zonisamide, stiripentol, oxcarbazepine, eslicarbazepine, rufinamide, lacosamide, retigabine, and perampanel. In many countries, women constitute the majority of users of these new AEDs.[5–7] This may be due to special, women-related safety and tolerability issues, but as well to the epidemiology of certain disease states.[8,9]

During the past 20 years, much attention has been directed toward AEDs and women. Hormonal and metabolic disturbances induced by AEDs, as well as teratogenic and adverse cognitive effects in the offspring of women with epilepsy have come into the spotlight.[10–13] Other women-specific questions such as drug interactions with hormonal contraception, the menstrual cycle, pharmacokinetic changes during pregnancy, breast-feeding, and menopause have also received growing attention.[14–18] Many studies on these issues have been conducted with the classic AEDs, mainly valproate and carbamazepine. With respect to the newer antiepileptic drugs however, only lamotrigine appears to be comparably well-studied. Other new AEDs have been examined only in part, or not at all.

Generally, and with only few exceptions (e.g., felbamate and vigabatrin), the new AEDs possess favorable safety profiles compared to the classic AEDs. Especially concerning hormone-related issues and teratogenicity, the new AEDs appear to come out better than the older AEDs.[19] Accordingly, the use of new AEDs by fertile women has increased considerably.[20]

Many of the studies discussed in this review, although useful, are small and do not qualify as basis for sound clinical guidelines. Their results should be reproduced by further, and preferably larger, studies. In fact, there are still too many gaps in our knowledge and much research remains to be done. Nonetheless, this review aims to give a brief yet concise overview on what is currently known, and what is not, on the clinical pharmacokinetics of new AEDs in women. Possible effects on the offspring of women treated with new AEDs (teratogenic or cognitive) will not be covered.

* Correspondence to: St. Olavs Hospital, Department of Clinical Pharmacology, Pb. 3250 Sluppen, 7006 Trondheim, Norway. Tel.: +47 72 82 91 09.
E-mail address: arne.reimers@legemidler.no

http://dx.doi.org/10.1016/j.seizure.2014.05.004
1059-1311/

2. Sex hormones

2.1. Endogenous female sex hormones

Female sex hormones can roughly be divided into estrogens and progestogens, and both of them can be of endogenous or exogenous origin. Estrogens have long been seen as pro-convulsive compounds while progestogens are generally thought to have anti-convulsive effects.[21–25] While this implies a theoretical possibility of pharmaco*dynamic* interactions with AEDs, things are not that simple. Estrogens may have neuroprotective and anti-convulsive effects as well. Their effects may depend on the body's general hormonal state, and fluctuations in the serum level ratio between estrogens and progestogens also seem to be of great relevance for the biological effects of estrogens.[25] Thus, with our limited knowledge, any net effect of the theoretical pharmaco*dynamic* interactions between estrogens, progestogens and AEDs would be difficult to evaluate or predict.

Pharmaco*kinetic* effects of endogenous female sex hormones on new AEDs are most relevant with respect to the menstrual cycle and pregnancy. These issues are discussed in separate sections below.

There are only very few studies on how new AEDs may exert effects on endogenous female sex hormones. Oxcarbazepine has been reported to decrease endogenous estrogen by 50% and progesterone by 58%.[26] For lamotrigine, only small and hardly clinically relevant changes (reduced estradiol and increased progesterone) have been found.[27] Levetiracetam does not seem to induce changes in female sex hormone status in prepubertal children or adult women.[28,29] There seem to be no published human studies investigating possible effects of topiramate, gabapentin, pregabalin or any of the other new AEDs on endogenous female sex hormones.

2.2. Exogenous female sex hormones

Exogenous female sex hormones are predominantly used in hormonal contraception and in hormonal replacement therapy (HRT). These are discussed in separate sections.

2.3. Endogenous male sex hormones

Women do produce male sex hormones. The most important ones are testosterone, androstendione, and dihydroepiandrosterone (DHEA). Alterations in their production may have significant consequences, e.g. disturbed metabolism or impaired fertility.

Testosterone is metabolised to estradiol by aromatase, and it has been assumed that levetiracetam may inhibit aromatase. If this is true, patients on levetiracetam may have raised testosterone levels, accompanied by reduced estradiol levels. In fact, this has been found in an in vitro study.[30] However, the only available study that investigated androgen and estrogen levels in women using levetiracetam found no differences vs. untreated controls.[28]

Lamotrigine apparently does not alter testosterone levels when compared to untreated controls or valproate-treated patients.[28,31,32] However, slightly reduced androstendione (22%) and elevated DHEA (30%) levels have been reported.[28]

Oxcarbazepine reduces testosterone levels by 25%, while DHEA and androstendione levels go up by 30% and 20%.[26]

In conclusion, with the exception of oxcarbazepine's effects on estradiol and progesterone, the impact of new AEDs on endogenous hormones – as far as they have been studied – seems to be rather moderate.

2.4. Sex hormone binding globulin

Sex hormone binding globulin (SHBG) is a liver-derived glycoprotein that transports sex hormones and regulates their access to target tissues.[33] AED-induced changes in SHBG levels may thus be relevant for sex hormone functioning and homeostasis. Lamotrigine has been shown not to affect SHBG levels significantly,[27,28,32,34] although Hill et al.[27] and Sidhu et al.[34] found lowered values in lamotrigine-treated women vs. controls. Likewise, levetiracetam does not seem to affect SHBG levels.[28] By contrast, oxcarbazepine increases SHBG by 10–20%. This effect may contribute to the lower levels of estradiol and progesterone found with oxcarbazepine treatment.[26] No data on SHBG *in women* are available for the other new AEDs.

3. Menstrual cycle

Estradiol up-regulates the expression of uridinediphosphate-glucuronosyltransferase (UGT) 1A4.[35] This enzyme catalyzes the metabolism of lamotrigine, and also retigabine/ezogabine. As shown by Sidhu et al.[34] (discussed below), the estrogen-mediated induction of UGT1A4 vanishes within a few days after stopping the intake of ethinyl estradiol containing contraceptives, and lamotrigine serum concentrations may double within one week. Similarly, physiological serum concentrations of endogenous estradiol vary considerably during the menstrual cycle. Extrapolating the findings of Sidhu et al.[34] one might expect similar ups and downs of lamotrigine levels. However, several studies show that fluctuating serum concentrations of endogenous estradiol or progesterone during the menstrual cycle do not affect lamotrigine serum concentrations in a clinically relevant manner.[36–38] Neither retigabine/ezogabine (also a UGT-substrate) nor any of the other new AEDs have been studied in this regard. However, during the luteal phase of the menstrual cycle, renal blood flow, glomerular filtration rate and body water may increase by up to 10%.[39] As is the case with, e.g. serum sodium or serum albumin, serum concentrations of most drugs, especially those with primarily renal elimination (e.g., gabapentin, pregabalin or levetiracetam) may decline accordingly, i.e. by a magnitude of 5–10%. Such changes are so small that they have to be regarded as clinically irrelevant. Unfortunately, as mentioned above, there is a substantial lack of data supporting these considerations.

4. Hormonal contraception

4.1. Effects of new AEDs on hormonal contraception

It is well known that traditional AEDs like phenytoin or carbamazepine can reduce the effect of hormonal contraception via induction of cytochome enzymes. Thus, it has become standard procedure during the development of new AEDs to examine their possible effects on hormonal contraception. Many of the new AEDs have been tested for possible impairment of hormonal contraception (Table 1). Lamotrigine, levetiracetam, gabapentin, zonisamide, lacosamide, perampanel and retigabine do not alter the serum concentrations of ethinyl estradiol.[34,40–46] Also, with the exception of lamotrigine and perampanel, they do not affect the serum concentrations of exogenous progestogens like levonorgestrel.[34,40] The effect of the latter two AEDs on progestogen levels seems to be rather modest. However, the possibility of decreased contraceptive efficacy cannot be excluded.[47,48] Oxcarbazepine and eslicarbazepine reduce exposure to both ethinyl estradiol and progestogens considerably, making hormonal contraception unreliable.[49,50] Topiramate is a moderate enzyme inducer. It has been examined in two studies, and in neither of them did it affect the kinetics of progestogens. With respect to ethinyl estradiol, one of these studies found no effect at daily topiramate doses of 50, 100 and 200 mg. However, the other study examined daily doses of 200, 400 and 800 mg, and here the maximum ethinyl estradiol

Table 1
Effects of hormonal contraception and new antiepileptic drugs on each other.

	Effect on:			
	AED	Ethinylestradiol	Progestogen	Reference
Lamotrigine	↓40–60%[a]	↔	↓19%	31,48,49
Levetiracetam	↔	↔	↔	42,50
Oxcarbazepine	n.a.	↓47%	↓47%	45
Eslicarbazepine	n.a.	↓30–40%	↓40%	44
Topiramate	n.a.	↓18–30%/↔	↔	46,47
Gabapentin	n.a.	↔	↔	40
Pregabalin	n.a.	n.a.	n.a.	
Zonisamide	↔	↔	↔	41,43
Lacosamide	↔	↔	↔	38
Retgabine/ ezogabine	↔	↔	↔	39
Stiripentol	n.a.	n.a.	n.a.	
Perampanel	n.a.	↔	↓40%	37

↔ No effect; n.a. = no data available.
[a] Lamotrigine reduced by ethinylestradiol-containing contraceptives.

serum concentration was reduced by topiramate at 400 mg and 800 mg daily.[51,52]

4.2. Effects of hormonal contraception on new AEDs

Sabers et al.[53] and others[34,54] demonstrated that oral contraceptives containing ethinyl estradiol can reduce the serum concentration of lamotrigine by over 50%, leading to breakthrough seizures and requiring dose adjustment. Progestogen-only contraceptives do not seem to affect lamotrigine pharmacokinetics significantly.[54] Despite its clinical relevance, this kind of drug interaction has received only modest attention. Levetiracetam, zonisamide, lacosamide and (somewhat surprising with regard to its UGT-mediated metabolism) retigabine/ezogabine have been found not to be affected by hormonal contraceptives.[41,42,44,45,55] No studies on the other new AEDs are available (Table 1).

5. Pregnancy

During pregnancy, significant changes in several physiological functions occur[56–58] and some of them will affect the pharmacokinetics of drugs given to the pregnant patient.[15,16,59] The most relevant changes are

(a) an increase by 50–80% of renal blood flow shortly after conception
(b) a massive increase in the serum concentration of endogenous estrogens and
(c) an increase in total body water and fat stores

Renal blood flow increases significantly as early as two weeks after conception and may lead to accelerated renal elimination of drugs, especially those that are excreted mainly unchanged through the kidneys. Raised estrogen levels lead to changes in metabolic capacity: dependent on the isoform, both increased and decreased activities of cytochome P450 (CYP) enzymes have been found. More importantly, raised estrogen induces the activity of UGT enzymes considerably.[35,58] This may lead to clinically relevant alterations in drug metabolism. Increased total body water and body fat may result in larger volumes of distribution and lower AED serum concentrations. Also, serum albumin concentrations decline considerably during pregnancy. However, lowered serum albumin usually affects drugs that are highly protein bound (>90%), leading to increases in their free (=pharmacologically active) fraction. Of the new AEDs, this applies to tiagabine and stiripentol. Unfortunately, no data on the course of their serum concentrations during pregnancy are available.[60] In addition to these changes, frequent vomiting makes drug absorption uncertain in many women.

The physiological changes induced by pregnancy are usually reversed within 1–2 weeks after childbirth. Changes in drug metabolism and elimination will also be reversed within this time frame, and serum concentrations that declined during pregnancy will rise after delivery. If dose adjustments were made during pregnancy, they must be reversed shortly, in order to prevent overdosing. Therapeutic drug monitoring is recommended.[59,61]

Lamotrigine is by far the best studied of all the new AEDs. Its serum concentrations decline by 40–60% during pregnancy, and most of this decline occurs already within the first trimester. Loss of seizure control occurs in up to 58% of pregnant women, and dose adjustment often becomes necessary.[62–71] Both increased renal elimination and increased metabolism contribute to this effect.[62,65,72] Serum concentrations turn back to pre-pregnancy levels within one to two weeks after delivery. An easy-to-follow algorithm for dose adjustment during pregnancy and its reversal after childbirth has been developed.[61]

Levetiracetam serum concentrations fall by 40–60% during pregnancy, most presumably due to accelerated renal elimination.[59,73,74] After delivery, concentrations raise to pre-pregnancy levels within one week.[73]

Topiramate concentrations decline by 30–40%, most likely due to accelerated renal elimination.[75,76] No serum concentrations have been measured within the first weeks after delivery, but one should expect a rapid reversal of pregnancy-induced changes in topiramate elimination, i.e. within 1–2 weeks.

Oxcarbazepine, or more precisely: its active metabolite licarbazepine (formerly called monohydroxyderivative, or MHD), declines by 30–40%.[77–79] The most active enantiomer of licarbazepine, S-licarbazepine (marketed as eslicarbazepine acetate), has not been studied separately. Because eslicarbazepine obviously follows the same elimination pathways as licarbazepine (i.e., mainly glucuronidation), a similar decline of its serum concentrations should be expected. This is supported by stereoselective measurements performed in a series of five patients treated with oxcarbazepine by Mazzucchelli et al.[77] In this case series, serum concentrations of S-licarbazepine increased 1.5–13-fold within a few days after delivery. A similar trend was seen for R-licarbazepine.

Zonisamide has not been studied systematically, but two case reports suggest that serum concentrations fall by 20–40% during pregnancy.[80,81] In one of these cases, the plasma concentration was measured after childbirth, and it rose by 45% within 9 days postpartum.[80]

Data on other new AEDs in pregnancy are not available (Table 2). It appears reasonable to assume that these drugs also are subject to more or less accelerated elimination from the body. Especially the serum concentrations of gabapentin, pregabalin and lacosamide (eliminated mainly unchanged via the kidneys) and retigabine/ezogabine (eliminated mainly by glucuronidation) should be expected to decline considerably.

Apart from the physiological changes leading to altered pharmacokinetics of new AEDs, one should keep in mind that adherence may have an even greater impact.[82] Several studies have shown that 40–60% of pregnant women do not take their medication as prescribed, and this has also been found in women with epilepsy.[83–86]

6. Breastfeeding

New AEDs, like other drugs, pass over into breast milk, although to varying degrees according to their individual physicochemical properties. Only a limited number of small-scaled studies and

Table 2
Changes in the serum concentrations of new antiepileptic drugs during pregnancy.

	Reduction in serum concentration	Reference
Lamotrigine	50–60%	56–63
Levetiracetam	40–60%	66,67
Oxcarbazepine	30–40%	70–72
Eslicarbazepine	n.a.	
Topiramate	30–40%	68,69
Gabapentin	n.a.	
Pregabalin	n.a.	
Zonisamide	20–40%	73,74
Lacosamide	n.a.	
Retgabine/ezogabine	n.a.	
Stiripentol	n.a.	
Perampanel	n.a.	

n.a. = no data available.

some case reports have been published. On the basis of what has been found so far, breastfeeding while taking new AEDs generally appears to be safe for the child.

Lamotrigine passage from blood into breast milk varies between 40 and 60%[66,87] and correlates with the mother's dose.[88] Neonatal lamotrigine serum concentrations are approximately equivalent to maternal lamotrigine concentrations at delivery. By contrast, the ratio of nursed infant/maternal serum lamotrigine concentrations is much lower and varies greatly, from 0.03 to 0.5. This does not seem to be related to the infant's age.[63,69,70,88] Possible causes include not only variable lamotrigine concentrations in breast milk, but also large interindividual differences in UGT1A4-mediated metabolic capacity up to the teen-age years (the younger the age, the greater the variability).[89] Indeed, it has been suggested that full UGT1A4 activity may not be reached before almost 19 years of age.[90] In sum, over 50 mother/infant pairs have been documented so far.[66,68–70,87,88,91–95] With only one exception, no adverse effects have been noted in these studies. The exception is a case report that describes an episode of apnoea in a breastfed child whose mother used a dose of 850 mg lamotrigine (increased from 450 mg during pregnancy).[95] At admission, 16 days postpartum, the infant's serum concentration was 4.9 μg/ml. However, on the day of birth and on postpartum day 3, infant serum concentrations were even higher (7.7 μg/ml and 5.8 μg/ml), but without any signs of respiratory depression or other adverse effects. This appears to be the only available report on acute adverse effects of breastfeeding while using lamotrigine and it should be noted that the dose used by the mother was relatively high. The maternal serum concentration on the day after admission of the infant was 14.9 μg/ml. Hence, the infant/mother serum concentration ratio was 0.3, which is within the usual range as reported by other authors. This case underlines the need to monitor maternal serum concentrations and to reduce the lamotrigine dose after delivery.

Possible cognitive effects have been investigated in a recent study with long-term follow-up. No difference in mean IQ between 30 breastfed and 36 non-breastfed children at age three years was found.[96]

Levetiracetam shows extensive transfer into breast milk and in two studies, the milk/maternal serum concentration ratio averaged around 1. Breast-fed infants had low levetiracetam serum concentrations, suggesting a rapid elimination of the drug. No adverse effects were noted.[74,97] By contrast, a single case report described increasing hypotonia and poor suckling in a 7 days old infant (born pre-term at 34 weeks of gestation) after levetiracetam had been added to his mother's treatment regime. In this case, the milk/plasma ratio was 3.1. No infant serum concentrations were measured at admission.[98]

From the sparse data available, the milk/maternal plasma concentration ratio of the active metabolite of oxcarbazepine, licarbazepine (MHD), is 0.5–0.8.[99,100] However, serum concentrations in the reported infants did not exceed 5% of the mother's plasma levels and no harmful effects have been reported.[99–104]

No separate studies on eslicarbazepine have been published.

Limited data suggest that topiramate is safe for breastfeeding. The milk/maternal plasma concentration ratio averages around 0.9, but serum concentrations in the infants were very low. No adverse effects on breastfed children have been reported.[105,106]

Only four mother/infant pairs have been reported with respect to zonisamide. The calculated milk/maternal serum concentration ratios ranged from 0.7 to 0.9.[80,107,108] No adverse effects on the breastfed child have been reported. However, because of the comparably high relative infant dose (about 30%) reported in these cases, caution and close monitoring of the infant is advisable.

Gabapentin concentrations in breast milk resemble the mother's plasma concentrations, with a milk/plasma ratio of 0.7–1.3. Infant plasma concentrations ranged from 6 to 12% of the mother's plasma concentration. No side effects in breastfed children have been observed, but only six mother/infant pairs are documented.[109,110]

There are no studies or case reports on the other new AEDs.

7. Menopause/hormone replacement therapy

Hormone substitution with natural or synthetic estrogens is very common in postmenopausal women. It has been reported that 50–71% of postmenopausal women with epilepsy experience a worsening of their seizures, and that the degree of worsening correlates with the estrogen dose.[111] This may be due to endocrine changes, but may also be a consequence of drug interactions between exogenous estrogens and AEDs.[112]

Three studies found lower lamotrigine serum concentrations and a higher clearance in postmenopausal women.[38,112,113] It might seem obvious that hormone substitution with estrogens may play a role. However, in one of these studies,[38] use of steroid hormones was an exclusion criterion. Further studies are needed to clarify this.

One study found that oxcarbazepine clearance does not seem to be affected by perimenopausal age.[114] No further data have been published.

No other studies on interactions between new AEDs and menopause or hormone replacement could be identified.

8. Bone health

Reduced bone mineral density and increased risk of fractures is a common adverse effect in women after long-term treatment with traditional AEDs.[115,116] Clinical data on the new AEDs are sparse. While a large retrospective cohort study ($n = 15\ 792$) reported an elevated bone fracture risk for gabapentin but none of the other new AEDs studied (including lamotrigine, levetiracetam and oxcarbazepine),[117] a smaller study with 560 participants (also retrospective) concluded that new AEDs are not associated with lower bone mineral density.[118] Other published data as well are conflicting.[119–124]. However, in an animal model, levetiracetam has been shown to impair bone quality but not bone density, suggesting that standard measurement of bone mineral density may not detect all AED-induced changes in bone health.[125] Further, prospective clinical studies, ideally with clinical outcome parameters such as bone fracture frequency, are needed in this field before any conclusions can be drawn.

9. Conclusion

Much research has been done, but even more research is needed. The speed at which new AEDs have been released during the past 20 years has led to a large number of available drugs which we know relatively little about when it comes to women-specific questions. As much as this review has tried to sum up the available knowledge, it has demonstrated how much we do not know (yet). Compared to traditional AEDs like phenytoin, phenobarbital or carbamazepine, most of the new AEDs have a more favorable safety profile even if some of them may affect hormone homeostasis or can induce serious adverse effects (e.g. felbamate, vigabatrin). Their clinical pharmacokinetics, however, may not be so favorable. Several women-specific factors may affect their serum concentration, and for many clinicians, therapeutic drug monitoring during pregnancy has virtually become a necessity. Finally, the example of lamotrigine serum concentrations being reduced by ethinyl estradiol containing contraceptives (discovered as late as 10 years after lamotrigine came onto the market) illustrates that future research on new AEDs and women may profit from new ways to look at things.

Conflict of interest statement

None declared.

Acknowledgement

I would like to thank Hanna Ljung, Department of Neurology, Skåne University Hospital, Lund, Sweden, for proof-reading of the manuscript.

References

1. Bialer M. Why are antiepileptic drugs used for nonepileptic conditions? *Epilepsia* 2012;**53**(Suppl. 7):26–33.
2. Johannessen Landmark C. Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy. *CNS Drugs* 2008;**22**:27–47.
3. Hamer HM, Dodel R, Strzelczyk A, Balzer-Geldsetzer M, Reese JP, Schoffski O, et al. Prevalence, utilization, and costs of antiepileptic drugs for epilepsy in Germany – a nationwide population-based study in children and adults. *J Neurol* 2012;**259**:2376–84.
4. Hsieh LP, Huang CY. Trends in the use of antiepileptic drugs in Taiwan from 2003 to 2007: a population-based national health insurance study. *Epilepsy Res* 2011;**96**:81–8.
5. Landmark CJ, Fossmark H, Larsson PG, Rytter E, Johannessen SI. Prescription patterns of antiepileptic drugs in patients with epilepsy in a nation-wide population. *Epilepsy Res* 2011;**95**:51–9.
6. Nicholas JM, Ridsdale L, Richardson MP, Ashworth M, Gulliford MC. Trends in antiepileptic drug utilisation in UK primary care 1993–2008: cohort study using the General Practice Research Database. *Seizure* 2012;**21**:466–70.
7. Pickrell WO, Lacey AS, Thomas RH, Lyons RA, Smith PE, Rees MI. Trends in the first antiepileptic drug prescribed for epilepsy between 2000 and 2010. *Seizure* 2014;**23**:77–80.
8. van Hecke O, Torrance N, Smith BH. Chronic pain epidemiology and its clinical relevance. *Br J Anaesth* 2013;**111**:13–8.
9. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Int J Methods Psychiatr Res* 2012;**21**:169–84.
10. Nadebaum C, Anderson V, Vajda F, Reutens D, Wood A. Neurobehavioral consequences of prenatal antiepileptic drug exposure. *Dev Neuropsychol* 2012;**37**:1–29.
11. Tomson T, Battino D. Teratogenic effects of antiepileptic drugs. *Lancet Neurol* 2012;**11**:803–13.
12. Verrotti A, D'Egidio C, Mohn A, Coppola G, Parisi P, Chiarelli F. Antiepileptic drugs, sex hormones, and PCOS. *Epilepsia* 2011;**52**:199–211.
13. Forsberg L, Wide K, Kallen B. School performance at age 16 in children exposed to antiepileptic drugs in utero – a population-based study. *Epilepsia* 2011;**52**:364–9.
14. Erel T, Guralp O. Epilepsy and menopause. *Arch Gynecol Obstet* 2011;**284**:749–55.
15. Harden CL, Pennell PB, Koppel BS, Hovinga CA, Gidal B, Meador KJ, et al. Management issues for women with epilepsy – focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels, and breast-feeding: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 2009;**50**:1247–55.
16. Tomson T, Landmark CJ, Battino D. Antiepileptic drug treatment in pregnancy: changes in drug disposition and their clinical implications. *Epilepsia* 2013;**54**:405–14.
17. Roste LS, Tauboll E, Svalheim S, Gjerstad L. Does menopause affect the epilepsy? *Seizure* 2008;**17**:172–5.
18. Burakgazi E, Harden C, Kelly JJ. Contraception for women with epilepsy. *Rev Neurol Dis* 2009;**6**:E62–7.
19. Molgaard-Nielsen D, Hviid A. Newer-generation antiepileptic drugs and the risk of major birth defects. *JAMA* 2011;**305**:1996–2002.
20. Bobo WV, Davis RL, Toh S, Li DK, Andrade SE, Cheetham TC, et al. Trends in the use of antiepileptic drugs among pregnant women in the US, 2001–2007: a medication exposure in pregnancy risk evaluation program study. *Paediatr Perinat Epidemiol* 2012;**26**:578–88.
21. Harrison NL, Majewska MD, Harrington JW, Barker JL. Structure-activity relationships for steroid interaction with the gamma-aminobutyric acidA receptor complex. *J Pharmacol Exp Ther* 1987;**241**:346–53.
22. Logothetis J, Harner R, Morrell F, Torres F. The role of estrogens in catamenial exacerbation of epilepsy. *Neurology* 1959;**9**:352–60.
23. Majewska MD, Harrison NL, Schwartz RD, Barker JL, Paul SM. Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor. *Science* 1986;**232**:1004–7.
24. Marcus EM, Watson CW, Goldman PL. Effects of steroids on cerebral electrical activity. Epileptogenic effects of conjugated estrogens and related compounds in the cat and rabbit. *Arch Neurol* 1966;**15**:521–32.
25. Scharfman HE, MacLusky NJ. The influence of gonadal hormones on neuronal excitability, seizures, and epilepsy in the female. *Epilepsia* 2006;**47**:1423–40.
26. Lofgren E, Tapanainen JS, Koivunen R, Pakarinen A, Isojarvi JI. Effects of carbamazepine and oxcarbazepine on the reproductive endocrine function in women with epilepsy. *Epilepsia* 2006;**47**:1441–6.
27. Hill M, Vrbikova J, Zarubova J, Kancheva R, Velikova M, Kancheva L, et al. The steroid metabolome in lamotrigine-treated women with epilepsy. *Steroids* 2011;**76**:1351–7.
28. Svalheim S, Tauboll E, Luef G, Lossius A, Rauchenzauner M, Sandvand F, et al. Differential effects of levetiracetam, carbamazepine, and lamotrigine on reproductive endocrine function in adults. *Epilepsy Behav* 2009;**16**:281–7.
29. Rauchenzauner M, Bitsche G, Svalheim S, Tauboll E, Haberlandt E, Wildt L, et al. Effects of levetiracetam and valproic acid monotherapy on sex-steroid hormones in prepubertal children – results from a pilot study. *Epilepsy Res* 2010;**88**:264–8.
30. Tauboll E, Gregoraszczuk EL, Wojtowicz AK, Milewicz T. Effects of levetiracetam and valproate on reproductive endocrine function studied in human ovarian follicular cells. *Epilepsia* 2009;**50**:1868–74.
31. Morrell MJ, Hayes FJ, Sluss PM, Adams JM, Bhatt M, Ozkara C, et al. Hyperandrogenism, ovulatory dysfunction, and polycystic ovary syndrome with valproate versus lamotrigine. *Ann Neurol* 2008;**64**:200–11.
32. Stephen LJ, Sills GJ, Leach JP, Butler E, Parker P, Hitiris N, et al. Sodium valproate versus lamotrigine: a randomised comparison of efficacy, tolerability and effects on circulating androgenic hormones in newly diagnosed epilepsy. *Epilepsy Res* 2007;**75**:122–9.
33. Hammond GL. Diverse roles for sex hormone-binding globulin in reproduction. *Biol Reprod* 2011;**85**:431–41.
34. Sidhu J, Job S, Singh S, Philipson R. The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. *Br J Clin Pharmacol* 2006;**61**:191–9.
35. Chen H, Yang K, Choi S, Fischer JH, Jeong H. Up-regulation of UDP-glucuronosyltransferase (UGT) 1A4 by 17beta-estradiol: a potential mechanism of increased lamotrigine elimination in pregnancy. *Drug Metab Dispos* 2009;**37**:1841–7.
36. Herzog AG, Blum AS, Farina EL, Maestri XE, Newman J, Garcia E, et al. Valproate and lamotrigine level variation with menstrual cycle phase and oral contraceptive use. *Neurology* 2009;**72**:911–4.
37. Reimers A, Brodtkorb E, Helde G, Spigset O. Lamotrigine serum concentrations throughout the menstrual cycle – a study of 2 cases. *Clin Neuropharmacol* 2006;**29**:160–2.
38. Wegner I, Edelbroek PM, Bulk S, Lindhout D. Lamotrigine kinetics within the menstrual cycle, after menopause, and with oral contraceptives. *Neurology* 2009;**73**:1388–93.
39. Brochner-Mortensen J, Paaby P, Fjeldborg P, Raffn K, Larsen CE, Moller-Petersen J. Renal haemodynamics and extracellular homeostasis during the menstrual cycle. *Scand J Clin Lab Invest* 1987;**47**:829–35.
40. Fycompa prescribing information. *U.S. Food and Drug Administration*. 2014. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202834lbl.pdf.
41. Cawello W, Rosenkranz B, Schmid B, Wierich W. Pharmacodynamic and pharmacokinetic evaluation of coadministration of lacosamide and an oral contraceptive (levonorgestrel plus ethinylestradiol) in healthy female volunteers. *Epilepsia* 2013;**54**:530–6.
42. Crean CS, Tompson DJ, Buraglio M. The effect of ezogabine on the pharmacokinetics of an oral contraceptive agent. *Int J Clin Pharmacol Ther* 2013;**51**:847–53.
43. Eldon MA, Underwood BA, Randinitis EJ, Sedman AJ. Gabapentin does not interact with a contraceptive regimen of norethindrone acetate and ethinyl estradiol. *Neurology* 1998;**50**:1146–8.
44. Griffith SG, Dai Y. Effect of zonisamide on the pharmacokinetics and pharmacodynamics of a combination ethinyl estradiol-norethindrone oral contraceptive in healthy women. *Clin Ther* 2004;**26**:2056–65.

45. Ragueneau-Majlessi I, Levy RH, Janik F. Levetiracetam does not alter the pharmacokinetics of an oral contraceptive in healthy women. *Epilepsia* 2002;**43**:697–702.
46. Sills G, Brodie M. Pharmacokinetics and drug interactions with zonisamide. *Epilepsia* 2007;**48**:435–41.
47. GlaxoSmithKline. *Lamictal summary of product characteristics (SPC)*. 2014. http://www.medicines.org.uk/emc/medicine/4228/SPC last updated 08/04/2014 [accessed 08.05.14].
48. Eisai. *Fycompa summary of product characteristics (SPC)*. 2013. http://www.medicines.org.uk/emc/medicine/26951/SPC/Fycompa+2mg%2c4mg%2c6mg%2c8mg%2c10mg%2c12mg+film-coated+tablets last updated 28/11/2013 [accessed 08.05.13].
49. Bialer M, Soares-da-Silva P. Pharmacokinetics and drug interactions of eslicarbazepine acetate. *Epilepsia* 2012;**53**:935–46.
50. Fattore C, Cipolla G, Gatti G, Limido GL, Sturm Y, Bernasconi C, et al. Induction of ethinylestradiol and levonorgestrel metabolism by oxcarbazepine in healthy women. *Epilepsia* 1999;**40**:783–7.
51. Doose DR, Wang SS, Padmanabhan M, Schwabe S, Jacobs D, Bialer M. Effect of topiramate or carbamazepine on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in healthy obese and nonobese female subjects. *Epilepsia* 2003;**44**:540–9.
52. Rosenfeld WE, Doose DR, Walker SA, Nayak RK. Effect of topiramate on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in patients with epilepsy. *Epilepsia* 1997;**38**:317–23.
53. Sabers A, Buchholt JM, Uldall P, Hansen EL. Lamotrigine plasma levels reduced by oral contraceptives. *Epilepsy Res* 2001;**47**:151–4.
54. Reimers A, Helde G, Brodtkorb E. Ethinyl estradiol, not progestogens, reduces lamotrigine serum concentrations. *Epilepsia* 2005;**46**:1414–7.
55. Sabers A, Christensen J. No effect of oral contraceptives on the metabolism of levetiracetam. *Epilepsy Res* 2011;**95**:277–9.
56. Anderson GD, Carr DB. Effect of pregnancy on the pharmacokinetics of antihypertensive drugs. *Clin Pharmacokinet* 2009;**48**:159–68.
57. Sturgiss SN, Dunlop W, Davison JM. Renal haemodynamics and tubular function in human pregnancy. *Baillieres Clin Obstet Gynaecol* 1994;**8**:209–34.
58. Isoherranen N, Thummel KE. Drug metabolism and transport during pregnancy: how does drug disposition change during pregnancy and what are the mechanisms that cause such changes? *Drug Metab Dispos* 2013;**41**:256–62.
59. Reisinger TL, Newman M, Loring DW, Pennell PB, Meador KJ. Antiepileptic drug clearance and seizure frequency during pregnancy in women with epilepsy. *Epilepsy Behav* 2013;**29**:13–8.
60. Johannessen Landmark C, Johannessen SI, Tomson T. Host factors affecting antiepileptic drug delivery-pharmacokinetic variability. *Adv Drug Deliv Rev* 2012;**64**:896–910.
61. Sabers A. Algorithm for lamotrigine dose adjustment before, during, and after pregnancy. *Acta Neurol Scand* 2012;**126**:e1–4.
62. Ohman I, Beck O, Vitols S, Tomson T. Plasma concentrations of lamotrigine and its 2-N-glucuronide metabolite during pregnancy in women with epilepsy. *Epilepsia* 2008;**49**:1075–80.
63. Pennell PB, Peng L, Newport DJ, Ritchie JC, Koganti A, Holley DK, et al. Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. *Neurology* 2008;**70**:2130–6.
64. Petrenaite V, Sabers A, Hansen-Schwartz J. Individual changes in lamotrigine plasma concentrations during pregnancy. *Epilepsy Res* 2005;**65**:185–8.
65. Reimers A, Helde G, Brathen G, Brodtkorb E. Lamotrigine and its N2-glucuronide during pregnancy: the significance of renal clearance and estradiol. *Epilepsy Res* 2011;**94**:198–205.
66. Tomson T, Ohman I, Vitols S. Lamotrigine in pregnancy and lactation: a case report. *Epilepsia* 1997;**38**:1039–41.
67. Tran TA, Leppik IE, Blesi K, Sathanandan ST, Remmel R. Lamotrigine clearance during pregnancy. *Neurology* 2002;**59**:251–5.
68. de Haan GJ, Edelbroek P, Segers J, Engelsman M, Lindhout D, Devile-Notschaele M, et al. Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. *Neurology* 2004;**63**:571–3.
69. Fotopoulou C, Kretz R, Bauer S, Schefold JC, Schmitz B, Dudenhausen JW, et al. Prospectively assessed changes in lamotrigine-concentration in women with epilepsy during pregnancy, lactation and the neonatal period. *Epilepsy Res* 2009;**85**:60–4.
70. Clark CT, Klein AM, Perel JM, Helsel J, Wisner KL. Lamotrigine dosing for pregnant patients with bipolar disorder. *Am J Psychiatry* 2013;**170**:1240–7.
71. Battino D, Tomson T, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al. Seizure control and treatment changes in pregnancy: observations from the EURAP epilepsy pregnancy registry. *Epilepsia* 2013;**54**:1621–7.
72. Ohman I, Luef G, Tomson T. Effects of pregnancy and contraception on lamotrigine disposition: new insights through analysis of lamotrigine metabolites. *Seizure* 2008;**17**:199–202.
73. Westin AA, Reimers A, Helde G, Nakken KO, Brodtkorb E. Serum concentration/dose ratio of levetiracetam before, during and after pregnancy. *Seizure* 2008;**17**:192–8.
74. Tomson T, Palm R, Kallen K, Ben-Menachem E, Soderfeldt B, Danielsson B, et al. Pharmacokinetics of levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. *Epilepsia* 2007;**48**:1111–6.
75. Westin AA, Nakken KO, Johannessen SI, Reimers A, Lillestolen KM, Brodtkorb E. Serum concentration/dose ratio of topiramate during pregnancy. *Epilepsia* 2009;**50**:480–5.
76. Ohman I, Sabers A, de Flon P, Luef G, Tomson T. Pharmacokinetics of topiramate during pregnancy. *Epilepsy Res* 2009;**87**:124–9.
77. Mazzucchelli I, Onat FY, Ozkara C, Atakli D, Specchio LM, Neve AL, et al. Changes in the disposition of oxcarbazepine and its metabolites during pregnancy and the puerperium. *Epilepsia* 2006;**47**:504–9.
78. Christensen J, Sabers A, Sidenius P. Oxcarbazepine concentrations during pregnancy: a retrospective study in patients with epilepsy. *Neurology* 2006;**67**:1497–9.
79. Petrenaite V, Sabers A, Hansen-Schwartz J. Seizure deterioration in women treated with oxcarbazepine during pregnancy. *Epilepsy Res* 2009;**84**:245–9.
80. Kawada K, Itoh S, Kusaka T, Isobe K, Ishii M. Pharmacokinetics of zonisamide in perinatal period. *Brain Dev* 2002;**24**:95–7.
81. Oles KS, Bell WL. Zonisamide concentrations during pregnancy. *Ann Pharmacother* 2008;**42**:1139–41.
82. Koren G. Pharmacokinetics in pregnancy; clinical significance. *J Popul Ther Clin Pharmacol* 2011;**18**:e523–7.
83. Hancock RL, Koren G, Einarson A, Ungar WJ. The effectiveness of Teratology Information Services (TIS). *Reprod Toxicol* 2007;**23**:125–32.
84. Lupattelli A, Spigset O, Nordeng H. Adherence to medication for chronic disorders during pregnancy: results from a multinational study. *Int J Clin Pharm* 2014;**36**:145–53.
85. Matsui D. Adherence with drug therapy in pregnancy. *Obstet Gynecol Int* 2012;**2012**:796590.
86. Nordeng H, Ystrom E, Einarson A. Perception of risk regarding the use of medications and other exposures during pregnancy. *Eur J Clin Pharmacol* 2010;**66**:207–14.
87. Liporace J, Kao A, D'Abreu A. Concerns regarding lamotrigine and breastfeeding. *Epilepsy Behav* 2004;**5**:102–5.
88. Newport DJ, Pennell PB, Calamaras MR, Ritchie JC, Newman M, Knight B, et al. Lamotrigine in breast milk and nursing infants: determination of exposure. *Pediatrics* 2008;**122**:e223–31.
89. Reimers A, Skogvoll E, Sund JK, Spigset O. Lamotrigine in children and adolescents: the impact of age on its serum concentrations and on the extent of drug interactions. *Eur J Clin Pharmacol* 2007;**63**:687–92.
90. Miyagi SJ, Collier AC. Pediatric development of glucuronidation: the ontogeny of hepatic UGT1A4. *Drug Metab Dispos* 2007;**35**:1587–92.
91. Gentile S. Lamotrigine in pregnancy and lactation. *Arch Womens Ment Health* 2005;**8**:57–8.
92. Ohman I, Vitols S, Tomson T. Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. *Epilepsia* 2000;**41**:709–13.
93. Page-Sharp M, Kristensen JH, Hackett LP, Beran RG, Rampono J, Hale TW, et al. Transfer of lamotrigine into breast milk. *Ann Pharmacother* 2006;**40**:1470–1.
94. Rambeck B, Kurlemann G, Stodieck SR, May TW, Jurgens U. Concentrations of lamotrigine in a mother on lamotrigine treatment and her newborn child. *Eur J Clin Pharmacol* 1997;**51**:481–4.
95. Nordmo E, Aronsen L, Wasland K, Smabrekke L, Vorren S. Severe apnea in an infant exposed to lamotrigine in breast milk. *Ann Pharmacother* 2009;**43**:1893–7.
96. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, et al. Effects of breastfeeding in children of women taking antiepileptic drugs. *Neurology* 2010;**75**:1954–60.
97. Johannessen SI, Helde G, Brodtkorb E. Levetiracetam concentrations in serum and in breast milk at birth and during lactation. *Epilepsia* 2005;**46**:775–7.
98. Kramer G, Hosli I, Glanzmann R, Holzgreve W. Levetiracetam accumulation in human breast milk. *Epilepsia* 2002;**43**:105.
99. Bulau P, Paar WD, von Unruh GE. Pharmacokinetics of oxcarbazepine and 10-hydroxy-carbazepine in the newborn child of an oxcarbazepine-treated mother. *Eur J Clin Pharmacol* 1988;**34**:311–3.
100. Pedersen B. Oxcarbazepine in breast milk. *17th international epilepsy congress*. 1987.
101. Eisenschenk S. Treatment with oxcarbazepine during pregnancy. *Neurologist* 2006;**12**:249–54.
102. Gentile S. Oxcarbazepine in pregnancy and lactation. *Clin Drug Investig* 2003;**23**:687.
103. Lutz UC, Wiatr G, Gaertner HJ, Bartels M. Oxcarbazepine treatment during breast-feeding: a case report. *J Clin Psychopharmacol* 2007;**27**:730–2.
104. Öhman I, Tomson T. Pharmacokinetics of oxcarbazepine in neonatal period and during lactation. *Epilepsia* 2009;**50**:239.
105. Gentile S. Topiramate in pregnancy and breastfeeding. *Clin Drug Investig* 2009;**29**:139–41.
106. Ohman I, Vitols S, Luef G, Soderfeldt B, Tomson T. Topiramate kinetics during delivery, lactation, and in the neonate: preliminary observations. *Epilepsia* 2002;**43**:1157–60.
107. Ando H, Matsubara S, Oi A, Usui R, Suzuki M, Fujimura A. Two nursing mothers treated with zonisamide: should breast-feeding be avoided? *J Obstet Gynaecol Res* 2014;**40**:275–8.
108. Shimoyama R, Ohkubo T, Sugawara K. Monitoring of zonisamide in human breast milk and maternal plasma by solid-phase extraction HPLC method. *Biomed Chromatogr* 1999;**13**:370–2.
109. Kristensen JH, Ilett KF, Hackett LP, Kohan R. Gabapentin and breastfeeding: a case report. *J Hum Lact* 2006;**22**:426–8.
110. Ohman I, Vitols S, Tomson T. Pharmacokinetics of gabapentin during delivery, in the neonatal period, and lactation: does a fetal accumulation occur during pregnancy? *Epilepsia* 2005;**46**:1621–4.

111. Harden CL, Herzog AG, Nikolov BG, Koppel BS, Christos PJ, Fowler K, et al. Hormone replacement therapy in women with epilepsy: a randomized, double-blind, placebo-controlled study. *Epilepsia* 2006;**47**:1447–51.
112. Harden CL. Hormone replacement therapy: will it affect seizure control and AED levels? *Seizure* 2008;**17**:176–80.
113. Tomson T, Lukic S, Ohman I. Are lamotrigine kinetics altered in menopause? Observations from a drug monitoring database. *Epilepsy Behav* 2010;**19**:86–8.
114. Wegner I, Wilhelm AJ, Sander JW, Lindhout D. The impact of age on lamotrigine and oxcarbazepine kinetics: a historical cohort study. *Epilepsy Behav* 2013;**29**:217–21.
115. Ensrud KE, Walczak TS, Blackwell T, Ensrud ER, Bowman PJ, Stone KL. Antiepileptic drug use increases rates of bone loss in older women: a prospective study. *Neurology* 2004;**62**:2051–7.
116. Lyngstad-Brechan MA, Tauboll E, Nakken KO, Gjerstad L, Godang K, Jemtland R, et al. Reduced bone mass and increased bone turnover in postmenopausal women with epilepsy using antiepileptic drug monotherapy. *Scand J Clin Lab Invest* 2008;**68**:759–66.
117. Jette N, Lix LM, Metge CJ, Prior HJ, McChesney J, Leslie WD. Association of antiepileptic drugs with nontraumatic fractures: a population-based analysis. *Arch Neurol* 2011;**68**:107–12.
118. Lee RH, Lyles KW, Sloane R, Colon-Emeric C. The association of newer anticonvulsant medications and bone mineral density. *Endocr Pract* 2012:1–22.
119. Bauer S, Hofbauer LC, Rauner M, Strzelczyk A, Kellinghaus C, Hallmeyer-Elgner S, et al. Early detection of bone metabolism changes under different antiepileptic drugs (ED-BoM-AED) – a prospective multicenter study. *Epilepsy Res* 2013;**106**:417–22.
120. Beniczky SA, Viken J, Jensen LT, Andersen NB. Bone mineral density in adult patients treated with various antiepileptic drugs. *Seizure* 2012;**21**:471–2.
121. Koo DL, Hwang KJ, Han SW, Kim JY, Joo EY, Shin WC, et al. Effect of oxcarbazepine on bone mineral density and biochemical markers of bone metabolism in patients with epilepsy. *Epilepsy Res* 2014;**108**:442–7.
122. Meier C, Kraenzlin ME. Antiepileptics and bone health. *Ther Adv Musculoskelet Dis* 2011;**3**:235–43.
123. Mintzer S, Boppana P, Toguri J, DeSantis A, Vitamin D. levels and bone turnover in epilepsy patients taking carbamazepine or oxcarbazepine. *Epilepsia* 2006;**47**:510–5.
124. Phabphal K, Geater A, Limapichat K, Sathirapanya P, Setthawatcharawanich S, Leelawattana R. Effect of switching hepatic enzyme-inducer antiepileptic drug to levetiracetam on bone mineral density, 25 hydroxyvitamin D, and parathyroid hormone in young adult patients with epilepsy. *Epilepsia* 2013;**54**:e94–8.
125. Nissen-Meyer LS, Svalheim S, Tauboll E, Reppe S, Lekva T, Solberg LB, et al. Levetiracetam, phenytoin, and valproate act differently on rat bone mass, structure, and metabolism. *Epilepsia* 2007;**48**:1850–60.