

FITS OF ADOLESCENCE

Does epilepsy make a turn for the worse when kids turn teens?

Grace Roxas

Contributing Writer

Epilepsy and adolescence seem a particularly volatile mix, with the onset of puberty a jarring physiological event unto itself. But the common fear that epilepsy among children approaching puberty will necessarily take a turn for the worse as they enter the stage appears to be unfounded, except for incidental circumstances like the effect of adult hormonal cycles on seizure activity.

Dr. Marilyn Ortiz of the Philippine Children Medical Center said that “rigorous studies” now refute the myth and clearly show that the incidence of epilepsy is not influenced by puberty. Speaking before the fifth National Epilepsy Congress in Tacloban City, Leyte, she cited a population-based study in Nova Scotia, Canada showing a halving of epilepsy incidence there, from 40/100,000 before the age of nine to 20/100,000 in puberty and adolescence.

Medical authorities as ancient as Hippocrates have long held the counter-intuitive notion that epilepsy takes a low profile amid the raging onset of adolescence. Modern research appears to bear this out, with a few studies cited by Ortiz showing either a tendency toward fewer seizures, or the present level holding steady despite possible neurological triggers of hormonal changes during puberty.

However, sexual maturation and sheer ageing may leave the teenager with epilepsy vulnerable in new ways as she takes on the concerns of an adult. “Hormonal changes during the menstrual cycle can have a profound effect on seizure activity,” Ortiz said. “And this can be evident during the adolescent period with many.”

The catamenial exacerbation of seizures, reported in 75 percent of women with epilepsy including those in their early teens, refers to the increase of seizures around the time of menstruation in connection with the changing ratio of estrogen to progesterone.

Persons with epilepsy are also more inclined to have reproductive endocrine disorders than others of similar age. Seizures are seen

to acutely affect the function of the hypothalamus-pituitary-gland axis, screwing up a woman’s ovulation, menstruation, and fertility. Polycystic ovarian syndrome is by far the most important disorder of this class, with the intake of the anticonvulsants valproic acid and carbamazepine alleged as a primary factor.

Some syndromes associated with epilepsy, notably benign melandric epilepsy, are known to end by adolescence, but other syndromes, especially idiopathic generalized epilepsy, kick in at just such a time. “It is not clear if puberty itself has an influence or if the timing of the remission or onset is related to some other factors such as age,” noted Ortiz.

In psychosocial terms, teenagers with epilepsy share many of the cares of young people saddled with a chronic condition before they can evolve the coping mechanism of an adult. Psychiatrist Portia Valles-Luspo said it can drag on the child’s accomplishment of developmental tasks, leading to a prolonged adolescent period.

“*Para silang nare-retard*. They tend to be overprotected and babied, to have less experience with their peers, and have fewer appropriate role models,” she said, adding that the attending neurologist or pediatrician would be in the best position to notice and remark on this.

The adolescent’s family history, temperament, and personality trait before getting sick are factors outside of the parameters of the condition that can affect the patient’s psyche as a person with epilepsy. Same with environmental factors concerning the family, school, and peers.

Valles-Luspo posited that, as a neurologic dysfunction, epilepsy and its accompanying conditions might put a teen at higher risk for mental-health and academic problems than with other chronic illnesses with no neurologic involvement. A study she cited showed 45 percent of children with new-onset epilepsy had psychiatric problems.

Brain structure and function abnormalities cause the neuropsychological deficits that drag on the child’s performance in school

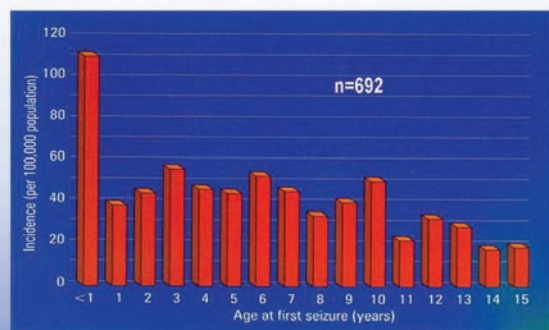
The adolescent with epilepsy: typical scenario

CONSIDER A TEEN-AGER WITH EPILEPSY:

- whose rapidly developing body often makes him/her self conscious about looks and appearances (I don’t want to take my pill for seizures because it makes me fat or hairy or bald);
- who is beginning to develop peer relationships and wants to belong (I don’t want others to know I have epilepsy because my friends might think I’m abnormal; I won’t take my medicine in school because I don’t want to be found out)
- who becomes romantically interested in boys or girls but is worried about being accepted (Who will love me if people find out I have epilepsy?)
- who is beginning to move away from parental control to a greater state of independence (I want to do things for myself, go out with my friends, but am often restricted by my parents who always fear something bad will happen to me when they’re not with me)
- who is beginning to ask himself “who am I” and “where do I fit in this universe” (I am an epileptic so what could I possibly contribute to the world?)

Management of epilepsy in adolescence is very challenging!

Incidence of epilepsy in childhood and adolescence: A population-based study in Nova Scotia 1977 to 1985



Decrease in incidence of epilepsy during pubertal years from 40/100,000 before age 9 years to 20/100,000 in puberty and adolescence

Camfield, et al. EPILEPSIA 37, 1996

Dr. Ortiz

Hormonal changes during the menstrual cycle can have a profound effect on seizure activity. And this can be evident during the adolescent period with many.



G.O. Miranda/In

Dr. Valles-Luspo

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G.O. Miranda/In

and other social settings. The more severe seizures are more likely to have sub-clinical reverberations leading to further problems.

High seizure frequency is the most important of the seizure-related variables linked to psychosocial problems. The other variables are the early age of onset, long duration of epilepsy, multiple seizure types, medications like barbiturates, and polytherapy.

The coping mechanism of a young person with epilepsy is also said to be taxed by more stressors than other children with no neurological deficits.

For a physician to optimize management of adolescent epilepsy, Ortiz highlights the importance of a correct seizure or epilepsy diagnosis. The choice of antiepileptic drug should not only hinge on appropriateness for the seizure type or epilepsy syndrome expe-

rienced by the patient but on the peculiar concerns of a teenager.

“If you are going to treat our teenagers, they are very conscious about their weight so they don’t like medications that make them fat. They also don’t like medications that make them too thin. They don’t like medications that make them not so pretty or handsome with the thickening of the gums, facial worsening, and hirsuteness,” she said. Their concerns as students and as women should also be considered as well as the ability to comply with the dosing.

Finally, the doctor has to relate well on the personal level through anticipatory guidance, talking to the patient honestly, without the parent present, to learn about issues with treatment, relationships, cognitive and athletic performance and even about contraception. **M**

Medicating women of seizure

Delicate treatment choices for women with epilepsy

Grace Roxas

Contributing Writer

As sexually responsible adults and new mothers, women taking medication for their epilepsy can face delicate treatment choices that need highly informed guidance from their physicians. Swedish neurologist Torbjörn Tomson elaborated on the finer points of antiepileptic drugs (AEDs) in contraception, pregnancy, and breastfeeding during a luncheon talk at the fifth National Epilepsy Congress.

Tomson showed the different directions of interaction between AEDs and contraceptives apart from the well-known effect of certain AEDs such as carbamazepine, phenobarbital, and phenytoin in watering down the potency of oral contraceptives.

Lamotrigine has a limited effect on the combined oral-contraceptive (COC) preparation. It mildly affects only the progestogen but not the estradiol component of the COC but it may have its own efficacy compromised by the estradiol, as shown by a finding that lamotrigine plasma concentration is only about 50 percent in women on oral contraceptives.

There are some AEDs—at least six of them—that do not affect oral contraceptives. Non-oral contraceptive methods—the Depo-Provera injection, intrauterine devices, and barrier methods—avoid colliding with the AEDs in the body system and are not diminished in efficacy as the oral.

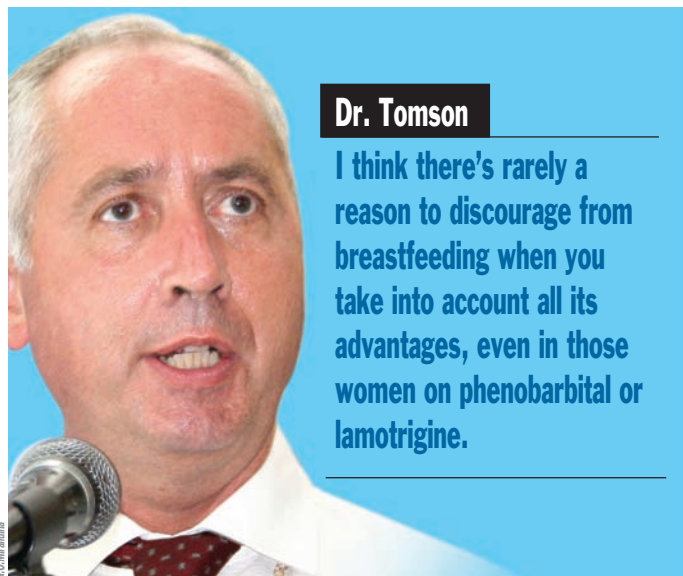
If oral contraceptives have to be given, Tomson recommends formulations with a high estrogen dose or continuing the dosing of oral contraceptive over the interval that is supposed to be pill-free by standard recommendation. Lamotrigine plasma levels should be monitored as per the patient's needs and changes in her contraception plans.

For pregnant women, Tomson also stressed the importance of closely looking at the drug levels for lamotrigine as well as for carbamazepine and phenytoin at least once each trimester to ensure that the dosing continues to protect the woman against seizures during her pregnancy. The neurologist should be on hand during the delivery of the child, as the return to the prepregnancy kinesis of the drug is very rapid, happening the day after delivery.

Tomson brought up the point that pregnancy comes with upward changes in the patient's metabolism and renal flow, the two crucial mechanisms that bear impact on how well the three aforementioned drugs and several others can continue to have a protective effect. He cited as highly convincing a US study showing a marked increase in seizure frequency, despite dosage adjustment, among pregnant women with a one-third or more decline in ratio of lamotrigine plasma concentration before and during pregnancy.

For a drug like phenytoin, the variability of individual patient responses is also a factor to consider, even if on the face of it, the net effect of pregnancy on the drug's efficacy, as gleaned through its active plasma concentration, is not that big.

When it comes to nursing mothers who take AEDs, Tomson holds



Dr. Tomson

I think there's rarely a reason to discourage from breastfeeding when you take into account all its advantages, even in those women on phenobarbital or lamotrigine.

Breastfeeding and Old AEDs

| AED | N | Milk/Plasma | Rel.dose* | Rel.conc.** |
|---------------|-----|-------------|-----------|-------------|
| Phenobarbital | >25 | 0.3-0.8 | 10-40% | 50-100% |
| Ethosuximide | >10 | 0.8-1.0 | 50-100% | 40-60% |
| Phenytoin | >25 | 0.1-0.6 | 7-10% | <10% |
| Carbamazepine | >25 | 0.3-0.6 | 3-8% | 10-20% |
| Valproate | >25 | 0.01-0.1 | 1-4% | <5% |

*Infant dose/kg bw as percentage of maternal dose/kg bw

**Plasma concentration in nursed infant relative maternal plasma levels

After Vinje 1997
Dr. Tomson

a firm line. "I think there's rarely a reason to discourage from breastfeeding when you take into account all its advantages, even in those women on phenobarbital or lamotrigine," he said. "What we should do is inform about the possibility, the small risks of such effects and be observant, so that in case they occur, you can make further investigations."

He noted that with these two drugs and with ethosuximide, clinically significant concentrations can sometimes reach an infant suckling from a mother under treatment. However, little or no adverse effects had been reported with these drugs among nursing infants concerned.

The effective level of drug concentration affecting the infant can get lost or camouflaged using some commonly followed guidelines, notably that of the US which only focuses on the milk/plasma concentration ratio, the actual drug amount excreted in breast milk.

"The infant's absorption, distribution, metabolism and elimination of the drug is also important because the newborn does not have the same kinetic process as an adult," Tomson explained. "And if you don't metabolize the drug, even a small intake may be too high a concentration." Therapeutic index and infant sensitivity to the drug are also factors to consider. **M**

GENERIC CAUTION

Patient education on generics may be more critical for physicians attending to patients with epilepsy than those with most other chronic conditions

Grace Roxas

Contributing Writer

“Epilepsy is unlike other medical conditions such as elevated cholesterol because of the seriousness of its symptoms. Breakthrough seizures after long remissions can have significant psychosocial and physical consequences,” said neurologist Bernardo Conde during a symposium on generic-drug substitution in the fifth National Epilepsy Congress.

A particular sticking point is the switch from branded antiepileptic drug (AED) to generic or from one generic drug to another, especially for patients who have already achieved reliable control over seizures. Conde pointed out that outside of bioavailability and bioequivalence problems leveled at generics, there really is no fundamental issue against using a generic drug as the initial treatment.

“The use of a single-source generic drug during initiation, titration, and maintenance of AED therapy would be cost-effective and would avoid concerns about generics,” he said. “However, switching can potentially lead to adverse effects of seizures.”

He added that medical management of epilepsy entails the complex need to slowly titrate doses. “There is a need for consistency of the product during titration to have predictable consequences. And this is a potential problem if there is a switch of product during titration.”

He cited international guidelines, including those from the American Academy of Neurology

and the Epilepsy Foundation that expressly advise against switching without the proper guidance of the physician, due to concerns about variations in the pharmacological properties of different formulations.

The Epilepsy Foundation raises the specter of reported breakthrough seizures among patients who made the switch. Conde also referred to a survey among neurologists on generics use wherein 56 percent of 301 respondents reported adverse events and 68 percent reported breakthrough seizures.

But neurologist Torbjörn Tomson, a resource speaker during the symposium, cautioned against putting too much credence on reports of adverse events, including breakthrough seizures, in connection with generic-drug intake.

“Remember that we don’t have a control group,” he says. “If you are told that there is an increase in the change to generics, they are more likely to report an adverse event. There’s a natural course to epilepsy. Seizures come and go. We are not likely to report that you



DR. CONDE
Need product consistency during titration.

are now seizure-free after having changed to generics. We are only likely to report the breakthrough seizures.”

He cited two Canadian studies that may signal, if not adverse event per se with a generic switch, then general dissatisfaction with that switch. In Canada, where generic substitution is compulsory, those who did stay with the generic version, particularly of lamotrigine, had a higher usage of AED and non-AED comedications and had a higher mean daily dose of lamotrigine itself. They also utilized more medical services, had more outpatient visits and longer hospital stays.

A North American case-control study showed an association between receiving hospital emergency care for epilepsy and a recent switch in formulation, either from brand to generic, generic to generic, or generic to brand.

In the Philippines, concerns surrounding generic AEDs might be more fundamental, affecting even the treatment-naïve patients, or those medicating for their epilepsy for the first time. Conde singled out valproate, phenytoin, and carbamazepine among a gen-

Odds ratio of having AED formulation switch 1.81 (1.25-2.63) for cases relative to controls

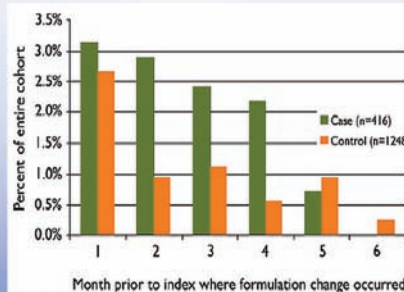


Figure 2. Percentage by month prior to index event of matched cases and controls experiencing an A-rated formulation change. Epilepsia © ILAE

Association demonstrated between receiving epilepsy care in emergency or inpatient and recent AED formulation switch causal relationship?

eral list of drugs with alleged bioavailability and bioequivalence problems.

Among AEDs, phenytoin has the added drawback of being the only AED with a narrow therapeutic index, said Tomson. A narrow index means that there’s a fine line between the toxicity and therapeutic levels of this drug. Conde said valproic acid and carbamazepine may also be toeing this fine line, and individual patients may have even narrower windows of tolerance for toxicity.

And then there are the bigger questions about the validity of the assays themselves. In Europe and the US, said Tomson, the validity of bioequivalence studies has been questioned because they were made in healthy subjects rather than on the elderly, patients taking other medications, and those with comorbidities.

He noted that the same brand may also change properties over time because of the change in the manufacturing process, a fact, he said, often lost on many physicians. **M**