

# Adverse Effects of Antiepileptic Drugs

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## ABSTRACT

Adverse effects of antiepileptic drugs (AEDs) are considered by patients to be at least as important as repetitive seizures in terms of quality of life. AED toxicity is frequent and contributes to a high proportion of treatment failures. Despite its high prevalence and clinical relevance, screening for adverse reactions to AEDs is not systematically included in everyday clinical practice; therefore it is very likely that it remains underestimated. Because there is little difference among AEDs in terms of efficacy, drug selection is often based on the adverse effects profile. AED toxicity is classified according to different parameters, such as severity, time of occurrence, organ system involvement, and mechanisms of action. Although most toxic reactions to drugs can be predicted from cumulative experience, prevention is not always possible, since multiple mechanisms and individual susceptibility to each drug participate in the final outcome. However, adverse effects can be reduced and appropriate action can be taken in time by means of a high degree of suspicion, knowledge of risk factors, and close follow-up. This article highlights factors to consider for detecting and managing AED adverse effects.

**KEYWORDS:** Adverse events, antiepileptic drugs

## CLASSIFICATION

Optimal management of epilepsy extends beyond seizure control. Adverse events of antiepileptic drugs (AEDs) are considered by patients to be at least as important as recurrent seizures when it comes to their quality of life. In fact, a large survey among patients with epilepsy showed that 35% gave priority to fewer adverse events over seizure control when asked to rate different areas of concern with respect to their epilepsy medication.<sup>1</sup> This perception is in sharp contrast with reports on the prevalence of AED-mediated adverse events. Adverse events are relatively common. In a multicenter European study that included 5211 patients, 88% reported at least one adverse event related to the medication they were taking,<sup>2</sup> which contributed to a change of AED in one third of patients. Toxicity is identified more frequently when clinicians ask about it directly than when it is

spontaneously reported by the patient.<sup>3</sup> Nevertheless, despite their high prevalence and clinical relevance, screening for AED-related adverse events is not systematically included in everyday clinical practice; therefore, it is very likely that adverse events often go undetected in regular patient care. Furthermore, since there is strong evidence of comparable AED efficacy in different epilepsies, adverse events are an important factor in the choice of AED for the individual patient.

Adverse events to AEDs include all reactions related to their administration, regardless of etiology. They can be classified according to severity, time of occurrence, organ system toxicity, and mechanisms involved. However, a pathophysiologic classification based on the mechanism of the adverse event is not realistic since these mechanisms are multifactorial and still poorly understood. A more practical classification is one that

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**Table 1 Classification of Side Effects of AEDs**

- Type A: Predictable, acute, and related to the mechanism of action of the drug
- Type B: Idiosyncratic, unpredictable, acute-subacute, and not related to the mechanism of action of the drug
- Type C: A consequence of the cumulative effect on long-term therapy
- Type D: Delayed, caused by teratogenic or carcinogenic mechanisms
- Type E: Pharmacodynamic or pharmacokinetic drug-to-drug interactions

AEDs, antiepileptic drugs.

considers the onset of the adverse event relative to the start of the AED, its relation to the dose and to time of dose intake, and the duration of symptoms (Table 1).<sup>4</sup>

### ACUTE CENTRAL NERVOUS SYSTEM ADVERSE EVENTS (TYPE A)

Acute adverse events are probably the most frequently recognized by patients and physicians, since they occur with almost every AED and are highly predictable. Characteristically, these reactions are dose-dependent and are usually explained by the mechanism of action of the agents. The most common acute central nervous system (CNS) AED-related adverse events include somnolence, dizziness, ataxia, diplopia, blurring of vision, fatigue, vertigo, and cognitive dysfunction. Treatment failure is the result of acute toxicity in ~20% of patients; this not only affects the quality of life of the patient, but it also can be responsible for the discontinuation of an AED that could have been effective. Initial high doses, rapid dose escalation, and co-administration with other drugs increase the risk of adverse events. They are more prominent at the beginning of treatment and are reversible upon dosage reduction or drug discontinuation. Frequently, tolerance to these adverse events develops over time and discontinuation of therapy is not required. Therefore, the premise “start low and go slow” applies to prevent AED-related adverse events.

Fluctuations in serum drug levels commonly exacerbate dose-dependent adverse events. These are typically time-locked to the dose schedule, when the peak plasma concentration is reached. For instance, diplopia, ataxia, and dizziness caused by carbamazepine (CBZ) or oxcarbazepine (OXC) occur usually within 20 minutes to 1 hour after drug administration. This phenomenon is known as “peak-of-dose” effect. Reduction of toxicity can be achieved by spreading the total daily dose throughout the day into more frequent intakes but at lower doses (e.g., by changing from a once-a-day or twice-a-day schedule to a three-times-a-day regimen) or by using a controlled-release preparation (when available).

Acute CNS side effects are more likely to occur in the elderly and in patients on polytherapy. In fact, treatment failure in older patients results more commonly from toxicity than from poor seizure control. Age-related physiologic changes, namely hypoalbuminemia, reduction of hepatic and renal drug clearance, and CNS changes, contribute to toxicity in this population even at low doses. Elderly patients benefit from lower daily doses and slower titration schedules, and are less likely to experience adverse events with the new or second-generation AEDs. For example, a systematic comparison between lamotrigine (LTG), gabapentin (GBP), and CBZ showed a better tolerance of these two new AEDs, supporting their use in elderly patients with newly diagnosed epilepsy.<sup>5</sup> Numerous reports have demonstrated that polytherapy is associated with an increase in adverse events; nonetheless, it appears that toxicity depends more on total drug load than on the number of compounds taken.<sup>6</sup> For this reason, it is better to use lower doses of each single drug when used in combination, rather than higher doses that would be reserved instead for monotherapy.

Cognitive difficulties are common in patients taking AEDs, and are frequently rated as the most worrisome adverse events. None of them is exclusive to any individual drug, as all AEDs, particularly when given at high doses, can produce cognitive adverse events. Cognitive adverse events are difficult to study since cognitive symptoms in patients with epilepsy may be caused by the underlying brain pathology, comorbidity, recurrent seizures, and social isolation, in addition to the AEDs. Comparative studies among drugs are difficult to perform, as their selection is based on the epilepsy syndrome and certain individual factors that already have an impact both on cognitive function and drug selection. Analysis in healthy volunteers could help in understanding the cognitive adverse effects of different AEDs; however, these studies are short and therefore do not allow for long-term evaluation after the adaptation period, when cognitive adverse events may be less pronounced. Nevertheless, observational and some controlled studies support that cognitive adverse events are more pronounced with barbiturates, benzodiazepines, and topiramate (TPM), while LTG, GBP, levetiracetam (LEV), tiagabine (TGB), and OXC have a more favorable cognitive profile. However, these data remain to be confirmed in different populations, especially those at greater risks of cognitive adverse events. In addition, in the process of drug selection it should always be considered that cognitive adverse events are quite variable among different patients because of differences in individual susceptibility.<sup>7</sup> When compared with other AEDs,<sup>7</sup> TPM has been associated with a higher incidence of decreased attention, verbal dysfunction, and memory impairment, adverse events that are often responsible for dose reduction or discontinuation of TPM. This AED seems to be better tolerated as monotherapy

**Table 2 Dose-Related Reactions Associated with Individual AEDs (Most Common Association)**

Arrhythmias	CBZ and PHT
Hyponatremia and water intoxication	CBZ and OXC
Metabolic acidosis, paresthesias, and oligohydrosis	ZNS and TPM
Macrocytosis and anemia related to folate deficiency	CBZ, PHT, and PHB
Tremor	VPA
Leukopenia	CBZ and PHT
Thrombocytopenia and abnormal platelet function	VPA
Insomnia	LTG and PHB

AEDs, antiepileptic drugs; CBZ, carbamazepine; PHT, phenytoin; OXC, oxcarbazepine; ZNS, zonisamide; TPM, topiramate; VPA, valproic acid; LTG, lamotrigine; PHB, phenobarbital.

than as adjunctive therapy. A study evaluated TPM as monotherapy for partial epilepsy and found a lower incidence of cognitive complaints than previously reported when used as add-on therapy.<sup>8</sup> This study did not find significant differences when a low maintenance dose (25 mg/d or 50 mg/d for patients weighing > 50 kg) was compared with much higher doses (200 mg/d or 500 mg/d for patients weighing > 50 kg). A past psychiatric history,<sup>9</sup> acute initial high doses, rapid dose titration, and implementation as add-on therapy have been consistently identified as the main factors contributing to TPM cognitive-related adverse events. Zonisamide (ZNS) may share similar cognitive effects as TPM, although further investigation is still required. Other relevant dose-related side effects are listed in Table 2.

## IDIOSYNCRATIC ADVERSE EVENTS (TYPE B)

Idiosyncratic AED adverse effects are due to individual inherent susceptibility to a particular drug and consequently cannot be anticipated on the basis of a known pharmacologic effect. Generally, they do not follow a predicted dose-effect profile and multiple mechanisms are involved.<sup>10</sup> Despite the effects' unpredictability, certain patients and drug characteristics are associated with a higher risk for idiosyncratic reactions. Individual susceptibility is higher in the pediatric and the elderly populations, patients with immune system diseases, certain infections, and inborn errors of metabolism. For certain idiosyncratic reactions, the risk can be minimized when treatment is started at a low dose followed by a slow titration.

## Cutaneous Reactions

AED-induced rash represents the most frequent of the idiosyncratic reactions. Although skin rashes may occur

**Table 3 Risk of Cutaneous Rash with AEDs<sup>11</sup>**

High Risk	Moderate Risk	Low Risk
PHT	OXC	LEV
LTG	TGB	GBP
CBZ	ZNS	VPA
	PHB	FBM
	Clobazam	TPM
		VGB
		Primidone

AEDs, antiepileptic drugs; PHT, phenytoin; OXC, oxcarbazepine; LEV, levetiracetam; LTG, lamotrigine; TGB, tiagabine; GBP, gabapentin; CBZ, carbamazepine; ZNS, zonisamide; VPA, valproic acid; PHB, phenobarbital; FBM, felbamate; TPM, topiramate; VGB, vigabatrin.

with every single AED (Table 3), the risk is highest with phenytoin (PHT) (10%), CBZ (8.7%) and LTG (6.2%).<sup>11</sup> Benzodiazepines, valproic acid (VPA), LEV, vigabatrin (VGB), TPM, and GBP are less commonly associated with this adverse event.<sup>11,12</sup> A high initial dose and rapid escalation increase the risk for cutaneous reactions, particularly for LTG. Other predictors of LTG-induced skin rash are its addition to VPA without adjusting the titration doses and rates to the slower clearance mediated by VPA. This adverse event has been reported more frequently in patients younger than 13 years.<sup>13</sup> On the other hand, in patients who have been on LTG for several months, the addition of VPA does not increase the risk of rash.

The risk of rash is also significantly higher for patients on PHT, CBZ, or LTG who have a previous history of rash to another AED.<sup>11</sup> There is cross-reactivity between OXC and CBZ, and 30% of patients who had a rash with CBZ can be expected to develop it with OXC. Fortunately, most skin reactions are benign and typically resolve within a few days of the drug discontinuation. Infrequently the rash can be more severe and present as Stevens-Johnson syndrome or toxic epidermal necrolysis. Both of these constitute a continuum, and although rare (1 to 10 per 10,000 new users) they are reported principally with aromatic AEDs (PHT, CBZ, and phenobarbital [PHB]) and LTG, and occur in the first 2 months of drug use.<sup>14</sup> These four compounds are also involved in the AED hypersensitivity syndrome, a life-threatening condition accompanied by systemic manifestations, characterized by the triad of fever, skin rash, and multiorgan damage. Predicting at the onset which cutaneous eruption will be self-limited and which will evolve to a severe skin reaction is not possible. However, certain clinical signs can be indicative of an ominous course and should be explored to identify those patients at risk for a malignant complication, such as Stevens-Johnson syndrome or toxic epidermal necrolysis. These signs include a painful rash, systemic manifestations (fever, lymphadenopathy, malaise, etc.), and/or mucosal involvement. In the presence of a cutaneous reaction, immediate drug

discontinuation is almost always recommended, and the patient should be switched to a drug with a low-risk profile (such as a benzodiazepine, LEV, or GBP). To minimize the risk of cross-reactivity, the new AED should be introduced once the rash has remitted. To minimize the exacerbation or recurrence of seizures with discontinuation of the AED, patients can be placed temporarily on a benzodiazepine like lorazepam. Admission to the hospital for close observation should be considered, especially in the presence of malignant signs. The efficacy of corticosteroid treatment has not been uniformly demonstrated, and its use is therefore controversial; however, if corticosteroids are used, slow withdrawal is advisable to avoid the reappearance of symptoms.

### Hepatotoxicity

Acute hepatitis is a rare but potentially fatal adverse event of VPA therapy which usually manifests within the first 3 months of therapy. Age younger than 2 years, polytherapy with enzyme-inducing AEDs, inborn errors of metabolism, previous hepatic disease, and mental retardation have been identified as variables mediating a potential higher risk of idiosyncratic hepatic reactions. Routine biochemical monitoring is not efficient for screening, since moderate elevation of liver enzymes (two- to threefold increase of ALT, AST, and GGT) or increased serum ammonia are common dose-related effects of VPA therapy and do not indicate a greater risk of liver damage. VPA-induced hepatotoxicity does not correlate with serum levels of this drug and onset of liver damage can be extremely acute; consequently, a normal laboratory test could be obtained shortly before fulminating liver failure develops.

Similar rates of hepatotoxicity have been attributed to felbamate (FBM), which has been reported to occur more commonly in female patients; other risk factors have not been identified with this AED.<sup>15</sup> Idiosyncratic liver toxicity is also described shortly after initiating treatment with aromatic AEDs and rarely with LTG, but rather than liver-specific toxicity, it is generally considered to be the expression of the AED hypersensitivity syndrome spectrum.

### Hematological Toxicity

Aplastic anemia is one of the most feared idiosyncratic complications of antiepileptic treatment. Patients on FBM are at a higher risk compared with other AEDs, albeit the degree of risk is not well defined (around 127 cases per million users).<sup>15</sup> FBM should be used with caution in patients with other immunological disorders, a history of a previous cytopenia, or allergy to other AEDs, as these increase the risk of an idiosyncratic reaction. In comparison, CBZ-associated incidence is

estimated at between 5 to 20 cases per million users.<sup>15</sup> CBZ and PHT have also been associated with the development of agranulocytosis.<sup>16</sup> Sporadic cases of other blood dyscrasias have been attributed to several AEDs. Mild decrease in leukocyte count is also common in patients on CBZ and PHT; this effect is usually dose-dependent, and does not indicate an increased risk for aplastic anemia. Similarly, decreased platelet count is also common during VPA therapy and not necessarily associated with altered coagulation function, unless the platelet count drops below 50,000 platelets/mL.

### Psychiatric Adverse Events

The risk of AED-mediated psychiatric adverse events is modest in relation to their efficacy. No AED is absent of these potential adverse effects, which although rare, are more common among patients with refractory epilepsy and those with a previous neurological or pre-existing psychiatric disorder. For instance, benzodiazepines and barbiturates, instead of sedating effects, may induce a paradoxical response consisting of irritability, hyperactivity, aggressiveness, and agitation. Barbiturates are also associated with elevated rates of mood disorders. Sedation and outbursts of psychotic episodes have been described with PHT at high doses. Treatment with VGB has been linked with increased rates of psychotic and depressive episodes.<sup>17</sup> A rapid-dose escalation, previous personal or family psychiatric history, and refractory epilepsy have all been found to increase the risk of affective and psychotic symptoms in patients taking TPM.<sup>18</sup> Aggressive behavior, irritability, and exacerbation of anxiety and depression have been noted with LEV. A history of febrile seizures was identified as a predictor of psychiatric adverse events both for TPM and LEV.<sup>18,19</sup> To prevent psychiatric reactions, a thorough evaluation of the patient's individual and family psychiatric histories is recommended when choosing an AED.

### Paradoxical Aggravation of Seizures

Exacerbation of seizures as an expression of a "paradoxical reaction" occurs when an AED increases the frequency of seizures, changes the pattern, and/or provokes new seizure types in individuals with seizure disorders expected to be responsive to the therapeutic effect of the AED. This inverse pharmacodynamic reaction occurs in the presence of a drug serum level within the "therapeutic" range and in the absence of any other clinical features suggestive of an encephalopathy or sedation. AEDs associated with the greatest risk of worsening seizures are those with a single mechanism of action, either GABAergic enhancement or blockade of Na<sup>+</sup> channels. Idiopathic and symptomatic generalized epilepsies as well as benign focal epilepsies of childhood are particularly prone to worsening with

**Table 4 AED-Induced Selective Aggravation of Seizures or Epilepsy Syndromes**

Drug	Syndrome/Seizure Type
PHT, CBZ, and OXC	Absences, myoclonic, atonic, and tonic seizures
PHB	Absences
VGB, TGB, GBP, PGB	Absences and myoclonia
LTG	Severe myoclonic epilepsy of infancy
CBZ, PHB, LTG	Benign focal epilepsy of childhood
Benzodiazepines	Tonic status in LGS
CBZ, LTG	ECSWS/Landau-Kleffner syndrome
CBZ, PHT	Progressive myoclonic epilepsies

AED, antiepileptic drug; PHT, phenytoin; CBZ, carbamazepine; OXC, oxcarbazepine; PHB, phenobarbital; VGB, vigabatrin; TGB, tiagabine; GBP, gabapentin; PGB, pregabalin; LTG, lamotrigine; LGS, Lennox-Gastaut syndrome; ECSWS, epilepsy with continuous spikes and waves during slow-wave sleep.

some AEDs (Table 4). Typical absences and myoclonic seizures are commonly reported to be aggravated or precipitated by OXC, PHT, TGB, VGB, pregabalin (PGB), and CBZ.<sup>20</sup> CBZ, OXC, PHT, LTG, and GBP can increase myoclonic seizures in patients with juvenile myoclonic epilepsy. CBZ has been the AED most frequently reported to cause myoclonus or absence status epilepticus when used in patients with idiopathic generalized epilepsies. Yet, the higher rate of reports (compared with other AEDs) may be related to its widespread use, rather than to a higher potential of CBZ to cause myoclonic and absence seizures.<sup>21</sup>

AED-related proconvulsant effects in specific epilepsy syndromes include myoclonic seizures in progressive myoclonic epilepsies, usually increased by the same drugs that aggravate idiopathic generalized epilepsies.<sup>22,23</sup> Treatment with LTG and CBZ may cause myoclonic status epilepticus and a deteriorating course in patients with Dravet syndrome.<sup>24,25</sup> Although rare, negative myoclonus, atypical absences, and evolution to electrical status epilepticus during sleep may be brought about by CBZ, LTG, and PHB in patients with benign rolandic epilepsy.<sup>26,27</sup> This view is not universally accepted and has been questioned, particularly by epileptologists in the United States. Benzodiazepines should be used cautiously in Lennox-Gastaut and West's syndrome, as they have been associated with status epilepticus, especially when administered intravenously.<sup>22,23</sup> Broad-spectrum AEDs, particularly VPA, appear to have a low potential for seizure aggravation.<sup>28</sup> Although rare, aggravation of seizures related to VPA may occur within the context of a VPA-provoked hyperammonemic encephalopathy, a misnomer as it is found as well with normal ammonia serum levels. To minimize the

risk of paradoxical reactions, selection of the appropriate AED should not be based solely on the type of seizure but rather on the epilepsy syndrome.

### Other Idiosyncratic Reactions

VPA-induced pancreatitis is an infrequent but life-threatening complication. It commonly occurs within the first year of treatment and with dosage increases, although it can also occur at any time during treatment.<sup>29</sup> Routine laboratory testing for serum amylase levels does not help identify patients at a higher risk, as isolated elevation of amylase is commonly found among asymptomatic VPA users. Inversely, VPA-induced pancreatitis with normal amylase levels is also described. When clinically suspected, determination of lipase blood levels is more helpful, and drug discontinuation is warranted.

Acute myopia and secondary angle closure glaucoma is a rare idiosyncratic reaction described in patients on TPM.<sup>30</sup> It occurs within the first month of treatment and affects both eyes. Ocular pain and hyperemia should alert the physician about this condition. Discontinuation of TPM is usually sufficient to normalize ocular pressure. Sporadic cases of systemic lupus erythematosus have been attributed to several AEDs, but principally to CBZ.<sup>31</sup> Contrary to other reactions, initiation of symptoms may occur several years after treatment. Whether this is coincidence in time or a true drug reaction is unclear; high titers of antihistone antibodies and resolution after drug withdrawal support a causative drug effect.

### LONG-TERM ADVERSE EVENTS (TYPE C)

Identifying long-term adverse events to AEDs requires a relatively large population exposed to the drug for an extended period of time. Therefore, they are better known among the first-generation AEDs than the newer agents. Long-term adverse events can involve multiple organs and have been related mostly to changes in endocrine and metabolic systems.

### Changes in Body Weight

The potential of AEDs to cause significant changes in body weight deserves careful consideration; AED-induced body weight changes can range from cosmetic concerns to clinically significant health risks. Furthermore, treatment compliance could also be influenced by changes in body image. Effects on body weight vary extraordinarily between drugs. Weight gain has been reported consistently with PGB, GBP, CBZ, VGB, and principally with VPA. The last AED is linked with the highest rates of obesity, both in pediatrics and in adults. Clinically relevant weight gain (> 10% compared with

pretreatment weight) was reported in 62% of patients on monotherapy with VPA.<sup>32</sup> Of note: VPA-induced augmentation of weight has been identified as early as the tenth week of initiation of treatment, and seems not to stabilize but to increase progressively in some patients as long as they are treated with the drug.<sup>32</sup> The increment of body weight varies broadly among patients and can lead to morbid obesity, facilitating the development of other conditions such as insulin resistance or polycystic ovarian syndrome. Clinical variables such as gender, age, dose, and pretreatment body weight have failed to identify those patients at a higher risk for weight gain.<sup>32</sup> When managing VPA-induced weight gain, dietary restriction and regular exercise appear not to be sufficient, and changing VPA to a weight-neutral AED is the preferable option when it is possible.

Weight loss is seen with FBM, ZNS, and most commonly with TPM. The degree of TPM-associated weight loss correlates both with pretreatment weight and with the dose employed.<sup>33,34</sup> In one study, weight reduction was maximal within the first 3 months for normal-weight and overweight patients. In obese patients, who experienced the greatest reduction, weight loss was stable over time and continued beyond the first 3 months up to 1 year (the length of the study).<sup>33</sup> When choosing weight-reducing AEDs one must consider that this adverse event may be desirable for obese patients, but detrimental for those at risk of malnutrition. If weight changes are a major concern, weight-neutral AEDs such as LTG and LEV are available options.

### Bone Health

Prolonged treatment with AEDs has been associated with a higher risk of fractures, osteoporosis, and rickets. Current evidence particularly stresses this association with enzyme-inducing AEDs such as PHT, CBZ, and barbiturates. This association probably results from an increased clearance of vitamin D and its metabolites by the P450 enzyme system. However, non-enzyme-inducing drugs such as VPA have also been found to increase bone resorption leading to a decrease in bone density, suggesting that other mechanisms are also at play. For example, rates as high as 23% for osteoporosis and 37% for osteopenia have been reported in patients who took VPA as monotherapy longer than 1 year.<sup>35</sup>

A women's community-based study<sup>36</sup> revealed a decline in bone density of nearly twofold among elderly women taking enzyme inducers, compared with age-matched women who did not take medication. As reported by others,<sup>37</sup> women older than 40 years who take enzyme inducers for more than 2 years could be at the greatest risk. Furthermore, the risk for osteopenia seems not to respect either age or gender, and has been reported as well in young epilepsy patients treated with AEDs.<sup>38</sup> Nevertheless, there are no comparative studies

supporting a protective effect of non-enzyme-inducing AEDs on bone health. There is no uniform consensus on how to monitor and prevent osteoporosis in patients at high risk. Periodic bone health screening (biochemical markers such as serum calcium, phosphate, PTH, and 25-OHD as well as follow-up bone densitometry) and supplementary treatment with bifosfonates, calcium, and/or high doses of vitamin D should be considered from the beginning when using AEDs that induce cytochrome P450.

### Sexual and Reproduction Function

Men with epilepsy on chronic treatment with PHT, CBZ, barbiturates, or VPA suffer most commonly from higher rates of sexual dysfunction caused by disturbances of reproductive endocrine function. Additionally, all four drugs and OXC are described to alter sperm morphology, motility, or concentration, and contribute to infertility in men.<sup>39,40</sup> VPA has also been linked with lower testicular volume in men with generalized epilepsy.<sup>40</sup> While sexual dysfunction with most of the new drugs has not been studied, LTG does not seem to alter male reproductive endocrine function, and changing to this drug can be an option when fertility problems or sexual dysfunction emerge in men with epilepsy.<sup>41,42</sup>

Both epilepsy itself and chronic treatment with AEDs are thought to be associated with reproductive endocrine dysfunction in women with epilepsy. The role of AEDs, particularly VPA, in women's reproductive function is still controversial.<sup>43</sup> Prevalence of reproductive endocrine dysfunction in women with epilepsy varies broadly among studies, reflecting differences in diagnostic criteria for polycystic ovary syndrome. However, many studies suggest that, compared with other AEDs, patients on VPA are at a higher risk for menstrual disorders, hyperandrogenism, and possibly for polycystic ovary syndrome.<sup>44-46</sup> Moreover, VPA-related weight gain is frequently observed together with polycystic ovary syndrome, and although lean women can be affected, this condition seems to be more common among obese patients.<sup>44</sup> It is reported as well that the risk of polycystic ovary syndrome or hyperandrogenism is elevated in young females with epilepsy on VPA when compared with age-matched nonusers.<sup>45,46</sup> Of note, endocrine sexual dysfunction in young women treated with VPA is reversed by discontinuation of the drug.<sup>45</sup> In line with this, replacement of VPA with LTG has been noted to normalize endocrine function in those women diagnosed with polycystic ovary syndrome or hyperandrogenism.<sup>47</sup>

### Visual Impairment

Visual field defects are causally related to long-term treatment with VGB. The prevalence of this complication varies among studies and upon the method of visual

assessment, reported in as high as 60% of patients in one study.<sup>48</sup> There is a male predominance, and both children and adults can be affected. The clinical picture is that of a bilateral asymptomatic peripheral reduction of visual fields with sparing of visual acuity; patients generally do not report visual deterioration: rather, they often complain of bumping into objects. There seems to be a cumulative effect, so that patients taking VGB at high doses for longer periods of time are potentially at risk.<sup>49</sup> The fact that the visual field defect can be irreversible stresses the need for visual peripheral screening on a regular basis.

### Other Chronic Adverse Events

Some AEDs are particularly related to well-recognized adverse events that are worth noting to prevent them. Drugs with carbonic-anhydrase inhibitor effects (ZNS, TPM, and acetazolamide) are associated with a modest increase in the incidence of kidney stones. The risk of nephrolithiasis is higher in the elderly, in patients with a previous or family history of kidney stones, and in patients with comorbidities on polypharmacy. Enforcing adequate hydration is particularly important in these population groups when treating them with ZNS, TPM, or acetazolamide. When nephrolithiasis occurs, discontinuation of the drug is normally sufficient to reverse the risk of this complication.

Movement disorders such as dystonia have been anecdotally attributed to PHT, CBZ, GBP, and FBM. Long-term exposure to PHT has been related to magnetic resonance imaging cerebellar atrophy,<sup>50</sup> particularly in elderly patients with high plasma concentration of the drug. The literature also abounds with cases of connective tissue disorders such as Dupuytren's contractures, frozen shoulder, palmar nodules, and joint pain in patients taking barbiturates. Reversibility of the contracture is unattainable once it is established. Cosmetic side effects also occur after long-term use of some AEDs. These include thinning of hair, alopecia, and change of hair color caused by VPA. Gingival hyperplasia and coarsening of facial features are common after prolonged treatment with PHT ("hydantoin facies") and may persist even after drug cessation.

### TERATOGENIC AND CARCINOGENIC ADVERSE EVENTS (TYPE D)

AED-related teratogenic effects are a major concern, both for prescribing clinicians and women with epilepsy. Congenital birth defects are classified according to severity as either major malformations or minor abnormalities. Retrospective case series have reported drug-specific syndromes after exposure to almost every single old drug. Nonetheless, most of them share many similarities and are often referred to as the fetal anticonvul-

sant syndrome, which combines major and minor malformations with other anomalies like intrauterine growth retardation, cognitive dysfunction, microcephaly, and in utero death. Prenatal exposure to AEDs is generally associated with a two- to threefold risk for major congenital malformations (MCM) compared with the general population (from the background risk of 1 to 2% to 4 to 9% with AEDs).<sup>51,52</sup> This hazard increases accordingly with the number of AEDs used during pregnancy, especially during the first trimester.<sup>52</sup> However, information as to which single drug has the safest teratogenic profile is still uncertain. Several large observational prospective studies are underway to clarify this issue.<sup>53-57</sup> They all highlight VPA as the drug associated with the highest risk of teratogenicity when compared with PHT, CBZ, and LTG as monotherapy, even though there is wide variation in the rate of malformations among different studies (6.2% to 20.29%<sup>54,55</sup>), probably reflecting differences in methodology and study population. VPA-related teratogenicity is significantly higher not only when combined with other AEDs, but also with doses over 1000 mg/day.<sup>53,54,58</sup> Preliminary data released from an ongoing study have found a rate of 6.5% MCM in pregnancies with exposure to PB monotherapy, stressing its potential teratogenicity.<sup>56</sup> Data from retrospective studies identified an increased risk of neuronal tube defects secondary to CBZ exposure. Prospective studies, however, have noted a low risk in CBZ-exposed children, with a teratogenicity risk similar to LTG (2.2%).<sup>55</sup> On the other hand, none of the new drugs but LTG have been tested with large numbers sufficient to assess their safety on human pregnancy. LTG monotherapy appears to be safe with rates of major birth defects comparable to risk estimates for the general population.<sup>55,59</sup> Yet, this advantage is lost when associated with VPA, which increased notably the rate of MCM to 12.5%.<sup>59</sup> This effect was attributable to VPA because LTG in polytherapy with other drugs did not significantly increase the risk (2.7%).<sup>59</sup> Of interest, the results of other studies suggest that there may be a dose-response effect of LTG and birth malformations, with a higher risk of MCM with doses over 200 mg/day,<sup>55</sup> although this finding has been reported in only one pregnancy registry (North American Registry), but not in the other four major registries.

Another issue that must be addressed is the possible negative effect of prenatal AED exposure in the cognitive development of children, which may not be completely recognizable until school age. This issue has been studied by different authors who identified learning problems and lower IQ more frequently in children exposed in utero either to polytherapy or VPA.<sup>60,61</sup> These findings led to a prospective multicenter study comparing the cognitive and behavioral development of children exposed to in utero monotherapy LTG, PHT, VPA, and CBZ. To date, the investigators have not

identified any impairment, either on verbal or nonverbal intelligence, in 2-year-old children exposed prenatally to CBZ (mean dose of 600 mg/day),<sup>62</sup> LTG, and PHT (see also the article by Kluger and Meador in this issue). On the contrary, VPA-exposed children showed a significantly lower verbal IQ. This was supported by another study which found a selective impairment of verbal IQ and memory functioning in school children whose mothers were on VPA during pregnancy.<sup>63</sup> This effect was not identified among kids exposed to PHT or CBZ. Yet, the issue of cognitive teratogenicity remains an open question, and data from more prospective trials are needed.

Not less disquieting is the potential for AEDs to be causally involved in increasing the risk of some types of cancer. Data gained from laboratory animal studies indicate uniformly that GBP, CBZ, PHT, and PB can facilitate the development of some tumors.<sup>64</sup> This is, however, felt to be species-specific and formal verification to suggest a similar risk in humans is lacking. The large experience with AEDs does not suggest a significant risk for developing cancer in humans; however, available evidence from long-term epidemiological studies and case-control series is poor and conflicting.<sup>65,66</sup> Chronic exposure to PB and PHT has been repeatedly reported to be possibly carcinogenic to humans. A higher risk for developing lymphoma has been attributed to long-term use of PHT, although this association needs further confirmation.<sup>67</sup> Moreover, this drug can as well produce "pseudolymphoma," a clinical condition that can only be distinguished from a true malignancy after drug removal. Phenobarbital has been associated inconsistently to brain and hepatic tumors. Information regarding VPA and carcinogenicity is sparser; polycystic ovary syndrome has been implicated as a potential risk factor for gynecological tumors. This association has not been described in humans on VPA regardless of the presence or absence of polycystic ovary syndrome. Alternatively, no carcinogenicity has been established for new drugs during regulatory testing development, but surveillance is required.

### PHARMACOKINETIC AND PHARMACODYNAMIC INTERACTIONS (TYPE E)

Drug-to-drug interactions are a frequent source of toxicity. The risk increases according both to the number of drugs used and the specific combinations employed. This issue has been addressed extensively in recent reviews.<sup>68,69</sup> In clinical practice, interactions caused by pharmacokinetic mechanisms are the most important ones; metabolic interactions, whether caused by enzyme induction or inhibition, account for the vast majority of the adverse effects reported. CBZ, PHT, and barbiturates are the three major hepatic enzyme-inducers which substantially augment the metabolism of those AEDs

that are fully or partly cleared by inducible enzymes. PHT and PHB can also increase the clearance of CBZ. In the same way, autoinduction of CBZ occurs after 3 to 4 weeks of treatment initiation. As a consequence, enzyme-inducing AEDs could decrease the therapeutic levels of the affected drugs and aggravate seizures. This effect is more pronounced for CBZ, TGB, LTG, and VPA, and both an increase in total daily dose and/or more frequent doses may be required. If a drug has an active metabolite, reduction of the drug serum levels can be paradoxically associated with an increased toxicity, mediated by an increase of this metabolite; for example, PHT and PB may lower CBZ concentrations but at the same time elevate CBZ-10,11-epoxide, which could result in toxicity. To a lesser extent, TPM and OXC possess enzyme-inducing properties. Because enzyme induction is reversible, there can be a rebound increase of the drug previously cleared once the inducing drug is removed. For instance, toxic levels of LTG or VPA can appear days to weeks after PB, CBZ, or PHT withdrawal. Clinicians should be aware of this deinduction period, as reduction of the dose of the coadministered drug may be needed days to weeks after the inducer has been removed.

Contrary to the above-mentioned reactions, interactions mediated by enzyme inhibition are a dose/concentration-dependent process that occurs in the hours after an inhibitor is added. This type of interaction is remarkably important when combining VPA with two AEDs, LTG and PB, in which the addition of VPA results in a decrement of their clearance. In the case of LTG, the degree of inhibition of LTG clearance is independent of the dose and concentration of VPA, beyond a dose of 500 mg/day.<sup>70</sup> At doses of 250 mg/day to 500 mg/day, the magnitude of inhibition is not uniform among all patients. Thus, a decrement of 50% of LTG clearance is reached both with 500 mg/day or higher doses of VPA. Accordingly, the addition of VPA to LTG should be accompanied by a concurrent 50% reduction of LTG's dose to avoid toxicity and maintain comparable serum concentrations. No further dose adjustments of LTG are necessary with further VPA dose increments. If VPA is introduced at doses between 125 mg/day and 375 mg/day, the dose of LTG should be lowered by 30%. However, patients should be instructed on the type of adverse events they can expect with high LTG serum concentrations, in which case they should lower the dose by an additional 20%.

VPA also inhibits the metabolism of CBZ-10,11-epoxide, while keeping the CBZ levels constant or lower. In general, toxicity is associated with 10,11-epoxide-CBZ/total CBZ ratios > 0.5. Relying on CBZ serum concentrations only without factoring in the 10,11-epoxide blood levels can result in misinterpretation of the patient's toxicity.

Among new drugs FBM, TPM, and OXC at high doses have been associated with inhibition of other AEDs. FBM's inhibition of the clearance of PHT, CBZ, PB, and VPA can result in toxicity, while the inhibitory effect of OXC and TPM is minimal.

Understanding of the potential pharmacokinetic and pharmacodynamic interactions between AEDs and other drugs is of great importance in clinical practice. On the one hand, enzyme induction caused by AEDs can lower critically the plasma concentration of antipsychotics, antidepressants, anticoagulants, chemotherapy agents, antimicrobials, birth control medications, and cardiovascular drugs, and thus decrease their efficacy. By the same token, AED serum concentrations can be increased or reduced by certain concomitant medications. To prevent drug-to-drug interactions, polytherapy should be reserved for those patients who have failed at least one trial of monotherapy. If not possible, selecting comedications which are less likely to interact is the best step. To that end, new AEDs are a preferable choice, as most of them do not affect the clearance of other AEDs or concomitant drugs. Monitoring of serum concentrations may be necessary when using AEDs with potential pharmacokinetic interactions.

## CONCLUSIONS

Adverse events caused by AEDs have a significant impact on the patient's quality of life. A systematic and careful identification of adverse events should be performed through all stages of epilepsy care. To anticipate their occurrence and set the appropriate clinical vigilance, it is important that patients and family members as well as every healthcare professional involved in their care be educated on the potential adverse events associated with the AED being prescribed. Education of the adverse events should be provided at the time of the office visit along with written material. In general, patients are more likely to tolerate an adverse event if they know ahead of time that it is possibly associated with the prescribed AED, than if it is a sudden occurrence that catches the patient and family unprepared. Clearly, adequate time has to be assigned during the office visit to explain the appropriate management of any potential adverse events, as well as to encourage patients and/or family members to report any new symptom that could be related to the AED.

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