Adverse effects of antiepileptic drugs

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More than 150 years after bromide was introduced as the first antiepileptic drug, adverse effects remain a leading cause of treatment failure and a major determinant of impaired health-related quality of life in people with epilepsy. Adverse effects can develop acutely or many years after starting treatment and can affect any organ or structure. In the past two decades, many efforts have been made to reduce the burden of antiepileptic drug toxicity. Several methods to screen and quantify adverse effects have been developed. Patient profiles associated with increased risk of specific adverse effects have been uncovered through advances in the areas of epidemiology and pharmacogenomics. Several new-generation antiepileptic drugs with improved tolerability profiles and reduced potential for drug interaction have been added to the therapeutic armamentarium. Overall, these advances have expanded the opportunities to tailor treatment with antiepileptic drugs, to enhance effectiveness and minimise the risk of toxic effects.

Introduction

Adverse effects are a leading cause of treatment failure with antiepileptic drugs. Not only do they result in early treatment discontinuation in up to 25% of patients, but also they preclude attainment of fully effective doses and have a negative effect on patient adherence.[1,2] Furthermore, adverse effects of antiepileptic drugs are a major source of disability, morbidity, and mortality[3] and a substantial burden on use and costs of health care.[4]

Although adverse effects have been recorded since the dawn of antiepileptic drug treatment, only in recent years has substantial effort been made to define, quantify, and address their clinical relevance. In 1985, the Veterans Administration Cooperative I trial compared the effectiveness of carbamazepine, phenobarbital, phenytoin, and primidone.

> "The outcome of this project underscores the unsatisfactory status of AED therapy with medications currently available. Most patients whose epilepsy is reasonably controlled must tolerate some side effects. These observations emphasize the need for new AEDs and other approaches to treatment."[5]

Systematic research into novel compounds, individualised antiepileptic drug regimens, and methods for assessment of toxic effects in everyday practice has resulted in more effective strategies to tackle adverse effects. Advances in epidemiology and pharmacogenetics have improved our understanding of the multifaceted aspects of antiepileptic drug toxic effects and allowed us to identify specific profiles of patients at increased risk for particular adverse effects.

In this Review, we discuss the adverse effect profiles of available antiepileptic drugs, highlight the clinical relevance of these side-effects, and provide practical recommendations for their prevention, assessment, and management. This is not a systematic review and reflects our own assessment of published work in this area and our personal experience of management of patients with epilepsy in specialised clinics.

Definitions, assessment, and prevalence

WHO defines an adverse drug effect as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function".[6] Distinction between the terms adverse effect and adverse event is important. An adverse effect is an untoward experience that can be attributed, directly or indirectly, to the drug. An adverse event is an untoward experience arising during treatment that is not necessarily caused by the drug.[7] In randomised or case-control studies, the probability of a drug causing a specific adverse effect can be inferred by comparison with a control group. In uncontrolled studies and when managing individual patients, however, to establish causality can be challenging, particularly when relevant information such as relation with dose, reversibility after drug discontinuation, and the effect of rechallenge is missing or incomplete.[7]

The frequency at which adverse effects of antiepileptic drugs are reported in a given population is dependent on the method of assessment, and every method has limitations. Reliance on unstructured interviews or spontaneous reporting underestimates the burden of antiepileptic drug toxic effects, whereas use of screening measures, such as questionnaires or checklists, can result in overestimation.[8] In a cross-sectional study undertaken in 56 epilepsy outpatient clinics in Spain, adverse effects of antiepileptic drugs were reported in 34% of patients when assessed by means of spontaneous reporting and in 65% when a checklist was used.[9] In an Italian multicentre study of 809 consecutive patients with drug-resistant epilepsy, the prevalence of adverse effects identified by a validated screening method—the adverse event profile—was almost three times greater than that detected with an unstructured interview (96% *vs* 37%).[10] Overall, depending on the population investigated, unstructured interviews or spontaneous reporting identify adverse effects in 10–40% of individuals with epilepsy on stable antiepileptic treatment,[11] whereas use of screening methods yields estimates of 60–90% or higher.[2,12]

Standardised methods to screen for adverse effects of antiepileptic drugs are available, some of which are adapted for children (table 1). These methods differ in scope, domains of toxic effects that are looked at, forms of administration, and length; thus, care should be taken in selection of the measure most appropriate for the

	Scope	Form of administration	Description	Estimated time of completion
Children				
Hague Side Effects Scale (HASES)[13]	To measure parents' perception of adverse effects of antiepileptic drugs in children with epilepsy	Parent completed	20 items assessing the frequency of the most common adverse effects of antiepileptic drugs during the previous 3 months, using a four-point Likert scale; item ratings can be summarised into two subscales and a total score; total scores range from 20 to 80, with higher scores indicating a greater burden of adverse effects	5 min
Pediatric Epilepsy Side-Effects Questionnaire (PESQ)*[14]	To measure patients' or parents' perception of adverse effects of antiepileptic drugs in children with epilepsy	Patient completed or parent completed	44 items assessing frequency of the most common adverse effects of antiepileptic drugs, using a six-point Likert scale; item ratings can be added to obtain a total score of 0–220, higher scores indicating more toxic effects	10 min
Adults				
Veterans Administration systemic toxicity rating scale[15]	To quantify impairment or change in physical status in patients starting an antiepileptic drug, exclusively in the setting of a clinical trial	Clinician completed	Eight major items assessing presence or absence of systemic adverse effects of antiepileptic drugs; in four items, a positive answer requires completion of additional items investigating the severity of specific signs or symptoms; all items are assigned a score (0–50) that is weighted on the importance of the adverse effects and the likelihood that the drug regimen would be discontinued; item ratings are added to calculate a total score, with scores ≥50 indicating that adverse effects are sufficiently serious to warrant discontinuation of the antiepileptic drug	10 min
Veterans Administration neurotoxicity rating scale[15]	To quantify impairment or change in neurological status in patients starting an antiepileptic drug, exclusively in the setting of a clinical trial	Clinician completed	11 items assessing severity of common neurotoxic adverse effects of antiepileptic drugs; items are assigned a score (0–50) that is weighted on the importance of the adverse effects and the likelihood that the drug regimen would be discontinued; item ratings are added to calculate a total score, with scores ≥50 indicating that adverse effects are sufficiently serious to warrant discontinuation of the antiepileptic drug	10 min
Adverse Event Profile (AEP)[16]	To measure patients' perception of adverse effects of antiepileptic drugs	Self-completed	19 items assessing the frequency of the most common adverse effects of antiepileptic drugs during the previous 4 weeks, using a four-point Likert scale; item ratings can be added to obtain a total score of 19–76, higher scores indicating a greater burden of adverse effects	5 min
A-B Neuropsychological Assessment Scale (ABNAS)†[17]	To measure patients' perception of cognitive adverse effects of antiepileptic drugs	Self-completed	24 items assessing severity of common cognitive adverse effects of antiepileptic drugs, using a four-point Likert scale; item ratings can be summarised into six subscales and a total score; total scores range from 0 to 72, higher scores indicating more severe drug-related cognitive dysfunction	5 min
Portland Neurotoxicity Scale (PNS)†[18]	To measure neurotoxicity complaints in patients on antiepileptic treatment	Self-completed	15 items investigating the severity of common neurotoxic adverse effects of antiepileptic drugs during the past few weeks, using a nine-point line scale; individual ratings can be summarised into two subscales or a total score; total scores range from 15 to 135, higher scores indicating more severe neurotoxicity	5 min
SIDe effects in AED treatment (SIDAED)‡[19]	To measure patients' complaints possibly related to antiepileptic treatment	Self-completed	46 items assessing severity of complaints possibly related to antiepileptic treatment, using a four-point Likert scale; the duration of every complaint is also scored; severity ratings can be summarised into ten categories and a total score; total scores are between 0 and 230, higher scores indicating more severe toxic effects	10 min

*Also referred to as the Cincinnati AED Side-Effects (CASE) Scale. †Can also be used in healthy volunteers receiving antiepileptic treatment. ‡Psychometric properties have not been reported.

Table 1: **Methods for screening adverse effects of antiepileptic drugs**

intended use. In the correct setting, screening methods have many advantages. First, they allow better definition and quantification of antiepileptic drug toxic effects in individuals. In a US study of 200 consecutive outpatients with epilepsy who completed the adverse event profile questionnaire, 88% reported at least one adverse effect, with a mean number of adverse effects per patient of 6·5.[2] Second, systematic screening of patients with validated methods aids reduction of antiepileptic drug toxic effects by optimisation of treatment, ultimately resulting in improved health-related quality of life.[20] Third, screening methods allow identification of populations at high risk for antiepileptic drug toxic effects. The burden of self-perceived toxic effects correlates with seizure control, being lowest in seizure-free individuals, intermediate in mixed populations from epilepsy clinics, and highest in those with drug-resistant epilepsy (table 2). These findings can be at least partly accounted for by the fact that drug-resistant patients are at increased risk of overtreatment, defined as an "unnecessary or excessive drug load…leading to a suboptimal risk-to-benefit balance".[27] Other risk factors for self-perceived antiepileptic drug toxic effects include polytherapy, comorbid mood disorders, female sex, childhood, and old age.[10,24,28]

Classification of adverse effects

Adverse drug effects can be classified by frequency, severity, symptoms, pathophysiological mechanisms, and affected organ or structure. We suggested previously[2] that classification based on patterns of co-occurrence is feasible and potentially useful to elucidate underlying mechanisms. By application of factor analysis to the 19 items of the adverse event profile, we found that adverse effects of antiepileptic drugs segregated into five distinct biologically plausible classes: cognition and

coordination; mood and emotion; sleep; tegument and mucosa; and weight and cephalalgia. The relevance of this classification was supported by the fact that increasing toxic effects within each class was associated with poorer health-related quality of life.

In this Review, we describe manifestations of antiepileptic drug toxic effects with a modified version of the WHO classification,[29] which distinguishes adverse effects into five types (table 3): acute, related to the pharmacological properties of the drug (type A); idiosyncratic (type B); chronic (type C); delayed (type D); and secondary to drug interactions (type E). This classification, similar to others, has limitations because attribution of an adverse effect to a specific class can be difficult and is open to interpretation. For example, topiramate-induced language difficulties, classified in the appendix (pp 1–3) as a type A effect, can develop insidiously over time in some individuals, at a pace similar to valproate-induced weight gain, a prototypical type C effect. Similar considerations can be applied to oligohidrosis and hyperthermia caused by topiramate and zonisamide. These effects are classified as type B because they seem to arise in only a few susceptible individuals. Although their underlying mechanisms are not understood fully, their appearance could be linked to inhibition of carbonic anhydrase, a mechanism that clearly causes a definite type A effect, such as topiramate-induced paresthesias.

See Online for appendix

Type A effects

Type A effects can be ascribed to the known mechanism of action of the drug; they usually arise at the beginning of treatment or after dose escalation and typically abate over time or after dose reduction. The most representative type A effects of antiepileptic drugs affect the CNS and include drowsiness, fatigue, dizziness, unsteadiness, blurred or double vision, difficulty concentrating, memory problems, irritability, and depression (table 3). Although adverse effect profiles vary from one drug to another, these effects are shared by most, if not all, antiepileptic drugs, which is particularly true for sedation and coordination disturbances (appendix pp 1–3).

Sedative effects, which range from mild drowsiness or tiredness to profound lethargy, are more frequent and severe with the older drugs phenobarbital, primidone, and benzodiazepines.[30] In the Veterans Administration Cooperative I trial,[5] in which the effectiveness of carbamazepine, phenytoin, phenobarbital, and primidone were compared as initial monotherapy for individuals with partial seizures, treatment failures were noted in 44–68% of patients across the four treatment groups. Adverse effects, particularly sedation and coordination disturbances, contributed substantially to at least 95% of treatment failures in the phenobarbital and primidone groups.[5]

Coordination disturbances include dizziness, unsteadiness, vertigo, imbalance, ataxia, gait difficulties, nystagmus, diplopia, and tremor. All first-generation antiepileptic drugs, particularly carbamazepine, phenytoin, primidone, and benzodiazepines, are associated with substantial risk of coordination difficulties.[30] However, these effects also arise with second-generation antiepileptic drugs. In a meta-analysis of randomised, placebo-controlled, adjunctive treatment trials of eight antiepileptic drugs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide), active treatment at any dose was associated with an almost three-fold increase in risk of coordination disturbances (unsteadiness, imbalance, or ataxia) compared with placebo.[31] Risk was particularly high for oxcarbazepine (risk ratio 4·70, 95% CI 2·61–8·45), lamotrigine (3·50, 2·06–5·96), topiramate (3·26, 2·11–5·03), and pregabalin (3·14, 1·37–7·19) whereas it was not increased significantly for levetiracetam or gabapentin at any dose. Among other second-generation antiepileptic drugs, eslicarbazepine acetate, lacosamide, and retigabine are also prone to dose-limiting adverse coordination effects.[32]

Cognitive dysfunction such as memory problems and difficulty concentrating are reported in up to 48% of patients with epilepsy on stable antiepileptic monotherapy.[12] Factors unrelated to treatment, however, can contribute to these estimates, including underlying cause and duration of epilepsy; type, frequency, and severity of seizures; post-ictal events; comorbid disorders, and psychosocial issues.[33] Of first-generation antiepileptic drugs, barbiturates and benzodiazepines have the most detrimental effects on cognition, which are typically accentuated in the setting of polypharmacy.[34]

	Country	Patients (n)	Seizure control*	Antiepileptic regimen	AEP scores†
Kwon and Park[21]	South Korea	150	All seizure-free	All on monotherapy	27·3 (8·2)
Carreño et al[22]	Spain	266	158 (59%) seizure-free, 108 (41%) uncontrolled seizures	Monotherapy and polytherapy (proportion unknown)	36·4 (9·7)
Perucca et al[2]	USA	200	58 (29%) seizure-free, 142 (71%) uncontrolled seizures	100 (50%) monotherapy, 100 (50%) polytherapy	38·8 (11·8)
Yue et al[23]	China	247	84 (34%) seizure-free, 163 (66%) uncontrolled seizures	148 (60%) monotherapy, 99 (40%) polytherapy	34·8 (9·0)‡
Martins et al[24]	Brazil	100	38 (38%) seizure-free, 62 (62%) uncontrolled seizures	29 (29%) monotherapy, 71 (71%) polytherapy	37·6 (13·3)
Chen et al[25]	Taiwan	357	185 (53%) seizure-free, 172 (47%) uncontrolled seizures	161 (45%) monotherapy, 196 (55%) polytherapy	30·7 (11·1)‡
Luoni et al[26]	Italy	809	All uncontrolled seizures (drug-resistant epilepsy)	182 (22%) monotherapy, 627 (78%) polytherapy	42·7 (11·4)§

AEP=adverse event profile. *Period of seizure outcome assessment varied across studies (3 months to 1 year). †All scores calculated for the 19-item version of the AEP unless otherwise specified (data are mean [SD]). ‡20-item version of the AEP. §21-item version of the AEP.

Table 2: **Mean AEP scores in patients with epilepsy on antiepileptic treatment, stratified by seizure outcome**

	Description	Examples	Prevention	Management
Type A	Related to the known mechanism of action of the drug; common (1–10%) or very common (>10%); acute; dependent on dose or serum concentration; predictable; reversible	Drowsiness, lethargy, tiredness, fatigue, insomnia; dizziness, unsteadiness, vertigo, imbalance, ataxia, diplopia, tremor; cognitive impairment; irritability, aggressive behaviour, depression; gastrointestinal symptoms; hyponatraemia; paresthesias	Select an antiepileptic drug with a profile of tolerability suitable to the characteristics and preferences of the patient; start at low doses; up-titrate gradually; target the lowest effective maintenance dose	Reduce dose; modify the dosing scheme; discontinue antiepileptic drug if measures to prevent or ameliorate toxicity are ineffective
Type B	Related to the individual vulnerability (immunological, genetic, or other mechanism); uncommon (0·1–1%) or rare (<0·1%); develop during the first few weeks of treatment; unpredictable; high morbidity and mortality; reversible	Skin rashes, severe mucocutaneous reactions (drug rash with eosinophilia and systemic symptoms, toxic epidermal necrolysis, Stevens-Johnson syndrome); aplastic anaemia, agranulocytosis; hepatotoxic effects, pancreatitis; angle closure glaucoma; aseptic meningitis	Avoid (or use very cautiously) specific antiepileptic drugs in high-risk groups; start at low doses; up-titrate gradually	Discontinue antiepileptic drug promptly; symptomatic or supportive management; substitute antiepileptic drug with least risk for cross-reactivity reactions or worsening of underlying condition
Type C	Related to the cumulative dose of the drug; common (1–10%); chronic; mostly reversible	Decreased bone mineral density; weight gain, weight loss; folate deficiency; connective tissue disorders; hirsutism, gingival hypertrophy; alopecia; visual field loss	Select an antiepileptic drug with a tolerability profile suitable to the characteristics and preferences of the patient	Symptomatic or replacement treatment (eg, calcium, vitamin D, folic acid) as needed; discontinuation of antiepileptic drug if required
Type D	Related to prenatal exposure to the drug (eg, teratogenesis) or carcinogenesis; uncommon (0·1–1%); delayed; dose dependent; irreversible	Birth defects; neurodevelopmental delay in the offspring; pseudolymphoma	If possible, avoid valproate, phenobarbital, and polytherapy in women of childbearing potential; aim at low-risk monotherapies at the lowest effective dose before pregnancy; avoid discontinuation or major treatment changes during pregnancy	..
Type E	Adverse drug interactions; common (1–10%); predictable; reversible	Increased risk of skin rash after adding lamotrigine to valproate; reduced seizure control after adding the combined contraceptive pill to lamotrigine; reduced effectiveness of warfarin after adding carbamazepine; increased risk for CNS neurotoxicity after combination of sodium-channel-blocking antiepileptic drugs	Avoid unnecessary polytherapy; choose concurrent drugs with low potential for adverse drug interactions	Adjust doses according to clinical response and, if necessary, drug concentrations in serum

***Table 3*: Adverse effects of antiepileptic drugs based on a modified version of the WHO classification**

Among newer antiepileptic drugs, topiramate seems to have a higher risk of attention difficulties and a specific effect on verbal function and language.[34]

Adverse psychiatric effects are noted in about 15–20% of patients with epilepsy who take antiepileptic drugs.[35] These effects include behavioural or personality changes (irritability, hyperactivity, agitation, and aggressive behaviour), depression, and psychosis.[36] In 2008, the US Food and Drug Administration (FDA) issued a warning of an increased risk for suicidal ideation and behaviour during treatment with antiepileptic drugs; this warning was based on findings of a meta-analysis of 199 trials of 11 antiepileptic drugs for different indications, including epilepsy and psychiatric disorders.[37] However, risk of adverse psychiatric effects varies considerably, and barbiturates, vigabatrin, tiagabine, topiramate, levetiracetam, zonisamide, and felbamate are associated with higher risks compared with other antiepileptic drugs.[36] Furthermore, growing evidence suggests that individual vulnerability plays an important part. For example, family and personal psychiatric history, family history of epilepsy, personal history of febrile convulsions, and presence of tonic-atonic seizures are independent predictors for occurrence of psychiatric symptoms during treatment with topiramate.[38] A positive psychiatric history seems to be an important risk factor for development of adverse psychiatric effects with other antiepileptic drugs.[39,40]

Type B effects

Often referred to as idiosyncratic, type B effects have been defined as adverse reactions that "cannot be explained on the basis of the known mechanism of action of the drug and occur mostly unpredictably in susceptible individuals only, irrespective of dosage".[41] Underlying mechanisms include direct cellular damage by the drug or its metabolites, immune-mediated hypersensitivity reactions, and, less frequently, interaction of the drug or its metabolites with atypical targets in the host organism.[42] Type B effects are less common than type A effects; they usually arise during the first few weeks of treatment and can be reversed after discontinuation of the drug. Delayed recognition and intervention, however, could carry a major risk of morbidity and even mortality (table 3).

The most common type B effects of antiepileptic drugs include cutaneous, haematological, and hepatic or pancreatic reactions (appendix, pp 1–3). Maculopapular rashes are noted in 5–17% of patients started on carbamazepine, phenytoin, phenobarbital, and lamotrigine.[43] Severe mucocutaneous reactions such as drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome, and toxic epidermal necrolysis affect 1–10 in 10 000 new users of these antiepileptic drugs.[44] Risk factors for cutaneous reactions include genetic predisposition, paediatric or old age, a previous history of cutaneous reactions with other drugs, high initial dose and rapid

escalation schedules, concomitant immune system disorders, and specific concurrent drugs.[42] Infectious diseases could also be implicated, as in the case of DRESS, in which reactivation of human herpes virus (HHV) 6 is suspected to have a pathogenetic role.[42] With respect to genetic predisposition, presence of the human leukocyte antigen *HLA-B*1502* is strongly correlated with carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in patients with ancestry across broad areas of Asia,[45,46] and evidence suggests these findings can also apply to phenytoin, lamotrigine, and oxcarbazepine.[47,48] Among other HLA genotypes that predispose to antiepileptic-induced reactions, the antigen *HLA-A*3101* has been found to be associated with multiple carbamazepine-induced cutaneous reactions in Chinese, Japanese, and European populations.[49,50]

Some antiepileptic drugs can cause life-threatening blood dyscrasias. For aplastic anaemia, the greatest risk is associated with felbamate, with an incidence of 127 cases per 1 000 000 users per year compared with two cases per 1 000 000 per year in the general population.[51] Predictors of felbamate-induced aplastic anaemia include a history of cytopenia, previous autoimmune disorders, and a positive antinuclear antibody titre.[52] Aplastic anaemia can also arise with other antiepileptic drugs. In a case-control study in which no patient on felbamate was included,[53] antiepileptic drug exposure was associated with a nine-fold increase in risk of aplastic anaemia. Most individuals were taking carbamazepine, valproate, or phenytoin.[53] Carbamazepine is also the antiepileptic drug with the highest potential for causing agranulocytosis. In a population-based study,[54] carbamazepine was associated with an odds ratio of 10·96 (95% CI 1·17–102·64) for developing this disorder. Rare cases have also been reported with phenytoin, valproate, and ethosuximide.[55]

Antiepileptic drug-induced hepatotoxic effects can occur in isolation or as part of DRESS.[42] In a US population-based study,[56] antiepileptic drugs were the fourth most common cause of drug-induced acute hepatic necrosis leading to liver transplantation, preceded only by paracetamol, isoniazid, and propylthiouracil. Felbamate and valproate carry the greatest risk for severe liver toxic effects. For felbamate, risk of fatal hepatic failure is estimated at one case per 26 000–34 000 exposures; for valproate, fatality estimates are about one per 10 000–49 000 for the combined population and one in 500 for high-risk paediatric patients (age <2 years, inborn metabolic disorders, and polytherapy).[52] Rare cases have been associated with carbamazepine, phenytoin, and lamotrigine.[57] Another serious complication of valproate is acute pancreatitis. Incidence of this disorder has been estimated at one case in 40 000, but this number could be under-reported.[58] Risk factors for valproate-induced pancreatitis include age younger than 20 years, polytherapy, chronic encephalopathy, and haemodialysis.[42]

For the **EURAP registry** see http://www.eurapinternational.org/

Type C effects

Type C effects include chronic reactions related to cumulative drug exposure (table 3). They can be insidious because of their slow progressive development.[59] Although some of these effects recede after discontinuation of the drug, others can be irreversible (appendix pp 1–3).

Changes in bodyweight are a typical type C effect, which can pose serious health hazards, impair self-esteem, and lead to non-adherence or discontinuation of treatment.[60] Weight loss can be caused by topiramate, zonisamide, felbamate, stiripentol, and rufinamide. Although potentially beneficial in overweight or obese individuals, weight loss can be problematic for nutritionally vulnerable patients.[61] Weight gain is most commonly associated with valproate, gabapentin, pregabalin, vigabatrin, retigabine, and to a lesser extent, carbamazepine, and carries an increased risk of hypertension, type 2 diabetes mellitus, dyslipidaemia, and cardiovascular disease.[60] Of note, preliminary evidence indicates that antiepileptic drugs, particularly enzyme-inducing drugs, could also increase the risk of cardiovascular disease independently of weight gain.[62] Moreover, long-term treatment with antiepileptic drugs can also cause abnormalities in bone health and lead to sexual dysfunction and reproductive disorders.[63] Decreased bone mineral density has been associated particularly with phenytoin and barbiturates, and can lead to an increased risk of fractures.[64] Carbamazepine and valproate can also have negative effects on bone health, but these findings are inconsistent.[65]

A serious type C effect is bilateral visual field loss induced by vigabatrin, which is irreversible[66] and can worsen with continued treatment.[67] Prevalence ranges from 14% to 92%.[68] Suggested risk factors include male sex, older age, cumulative dose and mean daily dose of vigabatrin, and duration of exposure.[66,69]

Type D effects

Teratogenic and carcinogenic effects are included in the type D category (table 3). Prenatal exposure to antiepileptic drugs, particularly in the first trimester, is associated with a two-fold to three-fold increase in frequency of major congenital malformations.[70] Risk is higher with polytherapy[70] and varies across antiepileptic drugs (appendix pp 1–3), with valproate and phenobarbital carrying a higher risk than carbamazepine, phenobarbital, and lamotrigine.[71,72] For valproate, the risk is clearly dose related, whereas for carbamazepine, phenobarbital, and lamotrigine, a relation with dose has been identified in the EURAP registry[73] but not in all studies.[71,74] Because of scant exposure data, the teratogenic potential of newer antiepileptic drugs other than lamotrigine is unclear, although some data indicate a higher risk with topiramate than with lamotrigine.[74]

For valproate, prenatal exposure also increases risk for impaired postnatal cognitive development.[75,76] To

date, no evidence shows conclusively that postnatal effects on cognitive development also arise with other antiepileptic drugs.[77]

Carcinogenic effects of certain antiepileptic drugs, most notably phenobarbital and phenytoin, were described in early animal studies, but evidence for the clinical relevance of these findings is inconclusive.[78] Long-term treatment with phenytoin, however, can cause so-called pseudolymphoma, a rare disorder that mimics clinically and histologically malignant lymphoma and resolves after discontinuation of the drug.[79] Misdiagnosis is not infrequent and can lead to unnecessary chemotherapy.[80] Rare cases of pseudolymphoma have also been reported with other antiepileptic drugs.[80]

Type E effects

Adverse drug interactions (type E effects) are common with epilepsy treatment (table 3) and are usually clinically relevant for several reasons. First, most antiepileptic drugs have a narrow therapeutic index, and small changes in pharmacokinetics results in reduced efficacy or increased toxic effects. Second, many antiepileptic drugs affect the activity of drug-metabolising enzymes. Third, most antiepileptic drugs are substrates of the same enzymes;[81,82] because these drugs are typically taken for many years, the probability is high that at some point in life, people with epilepsy will be exposed to interactions with other drugs used to treat intercurrent or concomitant disorders. Moreover, adverse drug interactions can arise when two or more antiepileptic drugs are co-prescribed, which is common in patients whose epilepsy is difficult to treat.

Adverse pharmacokinetic drug interactions are particularly common with first-generation antiepileptic drugs because they can induce or inhibit drug-metabolising enzymes (appendix pp 1–3). Enzyme induction takes place with carbamazepine, phenytoin, phenobarbital, and primidone. These drugs reduce the serum concentration and efficacy of a wide range of medications, including antimicrobials; immunosuppressants; oral contraceptives; cardiovascular, psychotropic, and antineoplastic drugs,[81] and other antiepileptic drugs.[82] Enzyme inhibition is caused most typically by valproate, which increases the serum concentrations of several other drugs, including phenobarbital and lamotrigine.[81,83] Serum concentrations of phenobarbital increase by 57–81% after addition of valproate. Inhibition of lamotrigine metabolism is at maximum with valproate doses of about 500 mg/day, which translates into a two-fold to three-fold increase in serum concentrations of lamotrigine if adjustments in dose are not made.[84]

Although the potential of most second-generation antiepileptic drugs for drug interaction is diminished, they are not free from clinically relevant interactions (appendix pp 1–3). For example, oxcarbazepine, lamotrigine, eslicarbazepine acetate, rufinamide, felbamate, and—at doses of more than 200 mg/day—topiramate can decrease the serum concentrations of some contraceptive steroids.[85] Oxcarbazepine also lowers the serum concentration of felodipine, although to a lesser extent than the fall caused by carbamazepine.[86] Felbamate, stiripentol, and—to a lesser extent—oxcarbazepine inhibit the metabolism of several concomitant antiepileptic drugs.[82] Similarly to older drugs, most second-generation antiepileptic drugs are substrates of drug-metabolising enzymes and are, therefore, vulnerable to enzyme induction and inhibition (appendix pp 1–3). Of the available antiepileptic drugs, only gabapentin and pregabalin seem not to cause or be a target for metabolic drug interactions.

Pharmacodynamic interactions at the site of action are also important in epilepsy treatment. In particular, growing evidence suggests that co-prescription of antiepileptic drugs that have the same primary mechanism of action can lead to potentiation of their respective neurotoxic effects (appendix pp 1–3).[82,83]

Special populations

Assessment of adverse effects can be challenging in young children, particularly those with associated intellectual disability. Yet, children can be more vulnerable to adverse effects than adults, and the toxic effect profile of specific antiepileptic drugs can differ between children and adults. In particular, behavioural difficulties (such as hyperactivity, insomnia, and aggression) induced by barbiturates or benzodiazepines happen more frequently in children than in adults.[30,34] Children are also at higher risk of idiosyncratic reactions. Incidence of lamotrigine-induced Stevens-Johnson syndrome has been estimated to be as high as one case in 100 children compared with three cases in 1000 adults.[87] Valproate-induced hepatotoxic effects are also more typical in paediatric populations, particularly infants younger than 2 years.[42]

At the other extreme of age, elderly people are also at increased risk of adverse effects, not only due to age-related changes affecting pharmacokinetics and pharmacodynamics—eg, decreased renal and metabolic function, impaired homoeostatic mechanisms, and increased sensitivity to CNS active drugs—but also because of possible interactions with drugs for comorbid disorders. In this population, antiepileptic drug-induced cognitive difficulties can exacerbate pre-existing cognitive deficits, whereas coordination disturbances can lead to falls and fractures.[34] Idiosyncratic reactions can also be more common in older individuals, particularly when appropriate precautions, such as use of lower starting and maintenance doses, are not taken. In a randomised trial in elderly people with newly diagnosed epilepsy, 25% of those receiving carbamazepine developed skin rashes that led to early withdrawal in about two-thirds of those affected.[88]

People with learning disabilities are another high-risk population because of potential factors predisposing them to antiepileptic drug toxic effects, such as

underlying brain damage, inborn errors of metabolism, and susceptibility to be prescribed inappropriate drug loads, including excessive polypharmacy.[27] Furthermore, individuals with learning disabilities are sometimes unable to report neurotoxic symptoms such as sedation, cognitive dysfunction, coordination difficulties, and visual disturbances.[89] Ascertaining whether behavioural changes indicate an underlying antiepileptic drug toxic effect can be challenging in these individuals.[34] At times, switching to a better tolerated antiepileptic regimen results in increased alertness and self-assertion, which can be misinterpreted as adverse behavioural effects.[89]

Women of childbearing potential need special consideration. In addition to teratogenic effects, antiepileptic drugs can cause reproductive endocrine disorders. Increased incidence of polycystic ovary syndrome and hyperandrogenism, for example, has been associated with valproate.[63] Interactions between antiepileptic drugs and oral contraceptives are another concern: enzyme-inducing antiepileptic drugs reduce the effectiveness of oral contraceptives,[83] whereas oral contraceptives increase clearance of lamotrigine and valproate, potentially leading to breakthrough seizures.[83] In particular, serum lamotrigine concentrations can fall by 50% after addition of a combined steroid oral contraceptive.[90] This interaction follows a cyclic pattern, with a drop in lamotrigine concentrations during the 21 days of pill intake and a striking increase during the 7-day pill-free interval.[90]

Adverse effects and health-related quality of life

Health is defined by WHO as "a state of complete physical, mental, and social wellbeing and not merely the absence of disease and infirmity".[91] Adverse effects of antiepileptic drugs have emerged as one of the strongest predictors of impaired health-related quality of life, independent of seizure outcome. In a representative study on the long-term psychosocial outcomes of childhood-onset epilepsy, individuals in remission on antiepileptic drug treatment had worse ratings for health-related quality of life compared with those no longer taking antiepileptic drugs.[92] In another study, 195 consecutive outpatients with epilepsy in neurology clinics were administered validated questionnaires to assess health-related quality of life (quality of life in epilepsy inventory 89), antiepileptic drug toxic effects (adverse event profile), and depression (Beck depression inventory).[93] Antiepileptic drug toxic effects were the strongest predictor of health-related quality of life, even after adjustments for age, sex, depression, and seizure frequency. Depressive symptoms also correlated with health-related quality of life, whereas seizure frequency did not. Identical findings were reported in a multicentre study from Italy.[26]

Identification and reduction of antiepileptic drug toxic effects can affect health-related quality of life positively.[20,94] In a randomised trial from the USA,[20] 62 patients with a high burden of antiepileptic drug toxic effects (adverse event profile scores of ≥45) were randomly assigned to two groups: in the first, clinicians had full access to the adverse event profile completed at every visit; in the second, clinicians were unaware of adverse event profile results.[20] After 4-month follow-up, patients whose clinicians were provided results of the adverse event profile showed a significant reduction in antiepileptic drug toxic effects compared with the other group, and this effect correlated with improved health-related quality of life. Notably, knowledge of adverse event profile scores was associated with a 2·8-fold increase (95% CI 1·7–4·8) in treatment changes, without any worsening of seizure control.

Prevention and management

Minimisation of the adverse effects of antiepileptic drugs is a multistage process that requires implementation of preventive measures, careful monitoring, and prompt interventions, as needed. For this approach to succeed, a "therapeutic alliance" between the patient and the clinician is essential. Patients must be actively involved in all aspects of their care, including selection of the most appropriate treatment, early detection of adverse effects, and decisions about corrective actions.

The first step to minimise occurrence of adverse effects of antiepileptic drugs is prevention, which starts with tailoring choice of drug to the characteristics of the individual. Attention must be given to risk factors for toxic effects. A previous psychiatric history, for example, cautions against use of antiepileptic drugs with potentially negative psychotropic effects, such as topiramate or levetiracetam. Likewise, individuals needing other drugs for associated disorders will benefit from receiving an antiepileptic drug with low potential for drug interactions. Other patient groups need special consideration too (table 3). For example, individuals of Asian ancestry in whom carbamazepine is considered should first be tested for *HLA-B*1502* and, if positive, an alternative antiepileptic drug should be prescribed.

The risk of adverse effects of antiepileptic drugs can be reduced by starting at a low dose and up-titrating gradually. Many adverse CNS effects can be minimised by gradual titration, owing to occurrence of pharmacodynamic tolerance.[95] Idiosyncratic reactions can also be diminished by use of low starting doses and gradual titration. In a pooled analysis of lamotrigine monotherapy trials,[96] incidence of rash was 6·1% when the dose in the first week of treatment was less than 31 mg/day, but it rose to 20·5% when the starting dose was 62·5–125 mg/day. Similar findings have been reported for carbamazepine and phenytoin.[95]

Because most adverse effects of antiepileptic drugs are dose dependent, efforts should be made to identify the lowest effective maintenance dose. This approach is particularly important in patients with newly diagnosed epilepsy, whose seizures are typically controlled in 50%

of cases with low-dose monotherapy.[1] In a case-control study of new-onset seizures,[28] individuals who were prescribed low-dose monotherapy reported very low rates of complaints suggestive of antiepileptic drug toxic effects, which did not differ substantially from those reported by patients who were not prescribed antiepileptic drugs.

The second step to minimise the adverse effects of antiepileptic drugs is regular clinical monitoring. Patients should be informed about alerting signs and symptoms of antiepileptic drug toxic effects, and their clinical status should be reviewed periodically. Use of screening methods for adverse effects of antiepileptic drugs (table 1) facilitates clinical monitoring and detection of subtle manifestations of toxic effects.[20] In some cases, measurement of serum concentrations of antiepileptic drugs can aid confirmation of toxic effects, particularly when subjective symptoms are difficult to assess, such as in children and individuals with learning disabilities.[97] Reference ranges of serum concentrations of antiepileptic drugs, however, have a purely probabilistic value, and diagnosis of toxic effects should be mainly clinical. The usefulness of blood chemistry and haematology tests has long been debated. Available evidence indicates that routine laboratory screening is neither cost-effective nor of value in asymptomatic individuals.[42] However, laboratory screening should at least be practiced in the following situations: before starting treatment, to establish a baseline against which to interpret any change in clinical status; in high-risk groups, including use of drugs with high potential for toxic effects, such as felbamate; in people with communication impairment; and when an idiosyncratic reaction is suspected.[42] For idiosyncratic reactions, specialised tests can be used depending on the nature of the reaction. In patients with manifestations seemingly restricted to one organ (eg, major skin rashes, hepatitis, pancreatitis), a full range of laboratory tests should be done to exclude broader involvement.

If adverse effects develop, management depends not only on the type of reaction but also on the individual. Most type A effects improve or even resolve with dose reduction. Intermittent CNS effects associated with excessive fluctuations in serum concentrations of antiepileptic drugs can be managed either by dividing the daily dose into more frequent administrations or, for specific antiepileptic drugs, by using a controlled-release formulation.[95] Typically, these measures are sufficient to restore optimum tolerability. In other patients, switching to a different antiepileptic drug with a different tolerability profile would be indicated. Although, for some patients, tolerable adverse effects are a necessary price to pay to maintain adequate seizure control, the risk of overtreatment should always be considered. Particularly in drug-resistant epilepsy, some patients can suffer more from the adverse effects of treatment than from manifestations of the disease.[27]

Severe type B reactions generally need immediate discontinuation of the drug. At least in patients on monotherapy, another antiepileptic drug should be introduced immediately to minimise risk of breakthrough seizures and status epilepticus. The substituted drug should preferably be suitable for rapid up-titration and bear the lowest risk of cross-reactivity with the drug that caused the reaction. Cross-reactivity happens most typically in structurally related compounds, such as aromatic antiepileptic drugs (phenobarbital, primidone, carbamazepine, phenytoin),[98] but it can also take place between aromatic antiepileptic drugs and lamotrigine.[99] Severe idiosyncratic reactions also require ad-hoc treatments. For example, Stevens-Johnson syndrome and toxic epidermal necrolysis should preferably be managed in a burn centre.[42]

Management of type C effects (table 3) should take into consideration the pathophysiology and reversibility of the disorder. Decreased bone-mineral density can benefit from vitamin D supplementation.[65] Megaloblastic anaemia associated with folate deficiency responds to folate replacement treatment.[95] For some type C effects such as weight gain, switching to another drug can help, particularly when alternative measures such as dietary control have failed.[60] Adverse drug interactions (type E effects) can usually be managed by appropriate dose adjustments.

Conclusions and future perspectives

Over the past few decades, advances in clinical trial methodology, drug surveillance systems, and understanding of pathophysiological mechanisms have permitted better characterisation of the adverse effect profile of individual antiepileptic drugs. In parallel, new knowledge has been acquired on risk factors for specific adverse effects and on strategies not only to minimise toxic effects, but also to improve their early detection and management. Doctors are increasingly aware of the importance of adverse effects as a determinant of health-related quality of life. Not surprisingly, tolerability and safety are generally regarded as a primary consideration for tailoring treatment choices to individual characteristics. The introduction of 15 novel antiepileptic drugs in the past 20 years has expanded opportunities to tailor

Search strategy and selection criteria

We searched PubMed up to June 7, 2012, with the terms: "adverse effects", "side effects", "adverse reactions", "tolerability", "toxicity", "safety", "antiepileptic drugs", "quality of life", "humans", and generic and brand key names of individual antiepileptic drugs. We also identified relevant published work by searching the reference lists of retrieved papers and from our own files. Only papers published in English were reviewed. The final reference list was generated on the basis of relevance to the broad scope of this Review.

treatment, and the improved tolerability profile of some of these drugs has had a positive effect on outcomes.[32]

Although major therapeutic advances have taken place, there is no room for complacency. For most second-generation antiepileptic drugs, inadequate data are available for important safety aspects such as teratogenic risk. For drugs introduced in recent times, available tolerability data are derived mainly from randomised trials undertaken in settings that are poorly representative of routine clinical practice and typically exclude patient groups at potentially the highest risk. Finally, serious adverse effects are often discovered long after an antiepileptic drug has been approved. For example, vigabatrin-induced visual-field defects were reported after 9 years of post-marketing use,[68] and an association between lamotrigine and aseptic meningitis, which prompted a warning by the FDA, has been suggested only recently.[100]

Despite these considerations, the future looks promising. Pharmacoepidemiological resources are being used increasingly to identify the individual profiles of patients at increased risk of specific adverse effects. Successes in pharmacogenetics are fuelling research into biomarkers of different aspects of antiepileptic drug toxic effects. Together with novel strategies to discover antiepileptic drugs with improved clinical profiles, these developments will ultimately result in better treatments for people with epilepsy.

Contributors

Both authors undertook the literature search and wrote the Review.

Conflicts of interest

We declare that we have no conflicts of interest.

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References

1 Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000; **342:** 314–19.

2 Perucca P, Carter J, Vahle V, Gilliam FG. Adverse antiepileptic drug effects: toward a clinically and neurobiologically relevant taxonomy. *Neurology* 2009; **72:** 1223–29.

3 Gilliam F, Carter J, Vahle V. Tolerability of antiseizure medications: implications for health outcomes. *Neurology* 2004; **63** (suppl 4)**:** S9–12.

4 Suh DC, Woodall BS, Shin SK, Hermes-De Santis ER. Clinical and economic impact of adverse drug reactions in hospitalized patients. *Ann Pharmacother* 2000; **34:** 1373–79.

5 Mattson RH, Cramer JA, Collins JF, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *N Engl J Med* 1985; **313:** 145–51.

6 World Health Organization. International drug monitoring: the role of national centres. *World Health Organ Tech Rep Ser* 1972; **498:** 1–25.

7 Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000; **356:** 1255–59.

8 Baker GA, Camfield C, Camfield P, et al. Commission on Outcome Measurement in Epilepsy, 1994–1997: final report. *Epilepsia* 1998; **39:** 213–31.

9 Carreno M, Gil-Nagel A, Sanchez JC, et al. Strategies to detect adverse effects of antiepileptic drugs in clinical practice. *Epilepsy Behav* 2008; **13:** 178–83.

10 Canevini MP, De Sarro G, Galimberti CA, et al. Relationship between adverse effects of antiepileptic drugs, number of coprescribed drugs, and drug load in a large cohort of consecutive patients with drug-refractory epilepsy. *Epilepsia* 2010; **51:** 797–804.

11 Collaborative Group for Epidemiology of Epilepsy. Adverse reactions to antiepileptic drugs: a multicenter survey of clinical practice. *Epilepsia* 1986; **27:** 323–30.

12 Baker GA, Jacoby A, Buck D, Stalgis C, Monnet D. Quality of life of people with epilepsy: a European study. *Epilepsia* 1997; **38:** 353–62.

13 Carpay HA, Arts WF, Vermeulen J, et al. Parent-completed scales for measuring seizure severity and severity of side-effects of antiepileptic drugs in childhood epilepsy: development and psychometric analysis. *Epilepsy Res* 1996; **24:** 173–81.

14 Morita DA, Glauser TA, Altaye M, Fordyce SR, Holder DL. The Cincinnati AED Side-Effect Scale (CASE Scale): development and validation of a tool to measure antiepileptic drug side effects objectively in children with epilepsy. *Epilepsia* 2003; **44** (suppl 9)**:** 279.

15 Cramer JA, Smith DB, Mattson RH, Delgado Escueta AV, Collins JF. A method of quantification for the evaluation of antiepileptic drug therapy. *Neurology* 1983; **33** (suppl 1)**:** 26–37.

16 Baker GA, Frances P, Middleton E, et al. Initial development, reliability, and validity of a patient-based adverse events scale. *Epilepsia* 1994; **35** (suppl 7)**:** 80.

17 Aldenkamp AP, Baker G, Pieters MS, Schoemaker HC, Cohen AF, Schwabe S. The Neurotoxicity Scale: the validity of a patient-based scale, assessing neurotoxicity. *Epilepsy Res* 1995; **20:** 229–39.

18 Salinsky MC, Storzbach D. The Portland Neurotoxicity Scale: validation of a brief self-report measure of antiepileptic-drug-related neurotoxicity. *Assessment* 2005; **12:** 107–17.

19 Uijl SG, Uiterwaal CS, Aldenkamp AP, et al. A cross-sectional study of subjective complaints in patients with epilepsy who seem to be well-controlled with anti-epileptic drugs. *Seizure* 2006; **15:** 242–48.

20 Gilliam FG, Fessler AJ, Baker G, Vahle V, Carter J, Attarian H. Systematic screening allows reduction of adverse antiepileptic drug effects: a randomized trial. *Neurology* 2004; **62:** 23–27.

21 Kwon OY, Park SP. What is the role of depressive symptoms among other predictors of quality of life in people with well-controlled epilepsy on monotherapy? *Epilepsy Behav* 2011; **20:** 528–32.

22 Carreno M, Donaire A, Falip M, et al. Validation of the Spanish version of the Liverpool Adverse Events Profile in patients with epilepsy. *Epilepsy Behav* 2009; **15:** 154–59.

23 Yue L, Yu PM, Zhao DH, et al. Determinants of quality of life in people with epilepsy and their gender differences. *Epilepsy Behav* 2011; **22:** 692–96.

24 Martins HH, Alonso NB, Vidal-Dourado M, et al. Are adverse effects of antiepileptic drugs different in symptomatic partial and idiopathic generalized epilepsies? The Portuguese-Brazilian validation of the Liverpool Adverse Events Profile. *Epilepsy Behav* 2011; **22:** 511–17.

25 Chen HF, Tsai YF, Shih MS, Chen JC. Validation of the Chinese version of the Liverpool Adverse Events Profile in patients with epilepsy. *Epilepsy Res* 2011; **94:** 45–52.

26 Luoni C, Bisulli F, Canevini MP, et al. Determinants of health-related quality of life in pharmacoresistant epilepsy: results from a large multicenter study of consecutively enrolled patients using validated quantitative assessments. *Epilepsia* 2011; **52:** 2181–91.

27 Perucca E, Kwan P. Overtreatment in epilepsy: how it occurs and how it can be avoided. *CNS Drugs* 2005; **19:** 897–908.

28 Perucca P, Jacoby A, Marson AG, et al. Adverse antiepileptic drug effects in new-onset seizures: a case-control study. *Neurology* 2011; **76:** 273–79.

29 Perucca E, Meador KJ. Adverse effects of antiepileptic drugs. *Acta Neurol Scand Suppl* 2005; **181:** 30–35.

30 Kennedy GM, Lhatoo SD. CNS adverse events associated with antiepileptic drugs. *CNS Drugs* 2008; **22:** 739–60.

31 Sirven JI, Fife TD, Wingerchuk DM, Drazkowski JF. Second-generation antiepileptic drugs' impact on balance: a meta-analysis. *Mayo Clin Proc* 2007; **82:** 40–47.

32 Fattore C, Perucca E. Novel medications for epilepsy. *Drugs* 2011; **71:** 2151–78.

33 Kwan P, Brodie MJ. Neuropsychological effects of epilepsy and antiepileptic drugs. *Lancet* 2001; **357:** 216–22.

34 Loring DW, Marino S, Meador KJ. Neuropsychological and behavioral effects of antiepilepsy drugs. *Neuropsychol Rev* 2007; **17:** 413–25.

35 Weintraub D, Buchsbaum R, Resor SR Jr, Hirsch LJ. Psychiatric and behavioral side effects of the newer antiepileptic drugs in adults with epilepsy. *Epilepsy Behav* 2007; **10:** 105–10.

36 Schmitz B. Effects of antiepileptic drugs on mood and behavior. *Epilepsia* 2006; **47** (suppl 2)**:** 28–33.

37 US Food and Drug Administration. Joint meeting of the Peripheral and Central Nervous Drugs Advisory Committee and the Psychopharmacologic Drugs Advisory Committee: briefing material. July 10, 2008. http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-00-index.html (accessed Feb 20, 2012).

38 Mula M, Trimble MR, Lhatoo SD, Sander JW. Topiramate and psychiatric adverse events in patients with epilepsy. *Epilepsia* 2003; **44:** 659–63.

39 Mula M, Trimble MR, Yuen A, Liu RS, Sander JW. Psychiatric adverse events during levetiracetam therapy. *Neurology* 2003; **61:** 704–06.

40 White JR, Walczak TS, Marino SE, Beniak TE, Leppik IE, Birnbaum AK. Zonisamide discontinuation due to psychiatric and cognitive adverse events: a case-control study. *Neurology* 2010; **75:** 513–18.

41 Franciotta D, Kwan P, Perucca E. Genetic basis for idiosyncratic reactions to antiepileptic drugs. *Curr Opin Neurol* 2009; **22:** 144–49.

42 Zaccara G, Franciotta D, Perucca E. Idiosyncratic adverse reactions to antiepileptic drugs. *Epilepsia* 2007; **48:** 1223–44.

43 Chadwick D, Shaw MD, Foy P, Rawlins MD, Turnbull DM. Serum anticonvulsant concentrations and the risk of drug induced skin eruptions. *J Neurol Neurosurg Psychiatry* 1984; **47:** 642–44.

44 Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. *Neurology* 2005; **64:** 1134–38.

45 Chung WH, Hung SI, Hong HS, et al. Medical genetics: a marker for Stevens-Johnson syndrome. *Nature* 2004; **428:** 486.

46 Chen P, Lin JJ, Lu CS, et al. Carbamazepine-induced toxic effects and *HLA-B*1502* screening in Taiwan. *N Engl J Med* 2011; **364:** 1126–33.

47 Man CB, Kwan P, Baum L, et al. Association between *HLA-B*1502* allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. *Epilepsia* 2007; **48:** 1015–18.

48 Chen YC, Chu CY, Hsiao CH. Oxcarbazepine-induced Stevens-Johnson syndrome in a patient with *HLA-B*1502* genotype. *J Eur Acad Dermatol Venereol* 2009; **23:** 702–03.

49 Ozeki T, Mushiroda T, Yowang A, et al. Genome-wide association study identifies *HLA-A*3101* allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. *Hum Mol Genet* 2011; **20:** 1034–41.

50 McCormack M, Alfirevic A, Bourgeois S, et al. *HLA-A*3101* and carbamazepine-induced hypersensitivity reactions in Europeans. *N Engl J Med* 2011; **364:** 1134–43.

51 Kaufman DW, Kelly JP, Anderson T, Harmon DC, Shapiro S. Evaluation of case reports of aplastic anemia among patients treated with felbamate. *Epilepsia* 1997; **38:** 1265–69.

52 Pellock JM, Faught E, Leppik IE, Shinnar S, Zupanc ML. Felbamate: consensus of current clinical experience. *Epilepsy Res* 2006; **71:** 89–101.

53 Handoko KB, Souverein PC, van Staa TP, et al. Risk of aplastic anemia in patients using antiepileptic drugs. *Epilepsia* 2006; **47:** 1232–36.

54 Ibanez L, Vidal X, Ballarin E, Laporte JR. Population-based drug-induced agranulocytosis. *Arch Intern Med* 2005; **165:** 869–74.

55 Andres E, Maloisel F. Idiosyncratic drug-induced agranulocytosis or acute neutropenia. *Curr Opin Hematol* 2008; **15:** 15–21.

56 Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug induced liver injury in the United States. *Liver Transpl* 2004; **10:** 1018–23.

57 Bjornsson E. Hepatotoxicity associated with antiepileptic drugs. *Acta Neurol Scand* 2008; **118:** 281–90.

58 Gerstner T, Busing D, Bell N, et al. Valproic acid-induced pancreatitis: 16 new cases and a review of the literature. *J Gastroenterol* 2007; **42:** 39–48.

59 Cramer JA, Mintzer S, Wheless J, Mattson RH. Adverse effects of antiepileptic drugs: a brief overview of important issues. *Expert Rev Neurother* 2010; **10:** 885–91.

60 Jallon P, Picard F. Bodyweight gain and anticonvulsants: a comparative review. *Drug Saf* 2001; **24:** 969–78.

61 Biton V. Effect of antiepileptic drugs on bodyweight: overview and clinical implications for the treatment of epilepsy. *CNS Drugs* 2003; **17:** 781–91.

62 Mintzer S, Skidmore CT, Abidin CJ, et al. Effects of antiepileptic drugs on lipids, homocysteine, and C-reactive protein. *Ann Neurol* 2009; **65:** 448–56.

63 Mintzer S. Metabolic consequences of antiepileptic drugs. *Curr Opin Neurol* 2010; **23:** 164–69.

64 Souverein PC, Webb DJ, Weil JG, Van Staa TP, Egberts AC. Use of antiepileptic drugs and risk of fractures: case-control study among patients with epilepsy. *Neurology* 2006; **66:** 1318–24.

65 Pack AM. Treatment of epilepsy to optimize bone health. *Curr Treat Options Neurol* 2011; **13:** 346–54.

66 Plant GT, Sergott RC. Understanding and interpreting vision safety issues with vigabatrin therapy. *Acta Neurol Scand Suppl* 2011; **192:** 57–71.

67 Hardus P, Verduin WM, Postma G, Stilma JS, Berendschot TT, van Veelen CW. Concentric contraction of the visual field in patients with temporal lobe epilepsy and its association with the use of vigabatrin medication. *Epilepsia* 2000; **41:** 581–87.

68 Wild JM, Ahn HS, Baulac M, et al. Vigabatrin and epilepsy: lessons learned. *Epilepsia* 2007; **48:** 1318–27.

69 Maguire MJ, Hemming K, Wild JM, Hutton JL, Marson AG. Prevalence of visual field loss following exposure to vigabatrin therapy: a systematic review. *Epilepsia* 2010; **51:** 2423–31.

70 Tomson T, Battino D. The management of epilepsy in pregnancy. In: Shorvon S, Pedley TA, eds. The blue books of neurology: the epilepsies 3. Philadelphia: Saunders Elsevier, 2009: 241–64.

71 Morrow J, Russell A, Guthrie E, et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2006; **77:** 193–98.

72 Harden CL, Meador KJ, Pennell PB, et al. Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology* 2009; **73:** 133–41.

73 Tomson T, Battino D, Bonizzoni E, et al, for the EURAP study group. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol* 2011; **10:** 609–17.

74 Hernández-Díaz S, Smith CR, Shen A, et al. Comparative safety of antiepileptic drugs during pregnancy. *Neurology* 2012; **78:** 1692–99.

75 Meador KJ, Baker GA, Browning N, et al. Effects of fetal antiepileptic drug exposure: outcomes at age 4·5 years. *Neurology* 2012; **78:** 1207–14.

76 Bromley RL, Mawer G, Love J, et al. Early cognitive development in children born to women with epilepsy: a prospective report. *Epilepsia* 2010; **51:** 2058–65.

77 Palac S, Meador KJ. Antiepileptic drugs and neurodevelopment: an update. *Curr Neurol Neurosci Rep* 2011; **11:** 423–27.

78 Singh G, Driever PH, Sander JW. Cancer risk in people with epilepsy: the role of antiepileptic drugs. *Brain* 2005; **128:** 7–17.

79 Jeng YM, Tien HF, Su IJ. Phenytoin-induced pseudolymphoma: reevaluation using modern molecular biology techniques. *Epilepsia* 1996; **37:** 104–07.

80 Choi TS, Doh KS, Kim SH, Jang MS, Suh KS, Kim ST. Clinicopathological and genotypic aspects of anticonvulsant-induced pseudolymphoma syndrome. *Br J Dermatol* 2003; **148:** 730–36.

81 Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: interactions between antiepileptic drugs and other drugs. *Lancet Neurol* 2003; **2:** 473–81.

82 Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs. *Lancet Neurol* 2003; **2:** 347–56.

83 Perucca E. Clinically relevant drug interactions with antiepileptic drugs. *Br J Clin Pharmacol* 2006; **61:** 246–55.

84 Kanner AM, Frey M. Adding valproate to lamotrigine: a study of their pharmacokinetic interaction. *Neurology* 2000; **55:** 588–91.

85 Crawford P. Interactions between antiepileptic drugs and hormonal contraception. *CNS Drugs* 2002; **16:** 263–72.

86 Baruzzi A, Albani F, Riva R. Oxcarbazepine: pharmacokinetic interactions and their clinical relevance. *Epilepsia* 1994; **35** (suppl 3)**:** S14–19.

87 Guberman AH, Besag FM, Brodie MJ, et al. Lamotrigine-associated rash: risk/benefit considerations in adults and children. *Epilepsia* 1999; **40:** 985–91.

88 Brodie MJ, Overstall PW, Giorgi L, for The UK Lamotrigine Elderly Study Group. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. *Epilepsy Res* 1999; **37:** 81–87.

89 Brodtkorb E. Management of epilepsy in people with learning disabilities. In: Shorvon S, Perucca E, Engel J Jr, eds. The treatment of epilepsy, 3rd edn. Oxford: Wiley-Blackwell, 2009: 219–30.

90 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:** 191–99.

91 World Health Organization. Definition of health. April 7, 1948. http://www.who.int/about/definition/en/print.html (accessed June 22, 2012).

92 Sillanpaa M, Haataja L, Shinnar S. Perceived impact of childhood-onset epilepsy on quality of life as an adult. *Epilepsia* 2004; **45:** 971–77.

93 Gilliam F. Optimizing health outcomes in active epilepsy. *Neurology* 2002; **58** (suppl 5)**:** S9–20.

94 Uijl SG, Uiterwaal CS, Aldenkamp AP, et al. Adjustment of treatment increases quality of life in patients with epilepsy: a randomized controlled pragmatic trial. *Eur J Neurol* 2009; **16:** 1173–77.

95 Zaccara G, Balestrieri F, Ragazzoni A. Management of side-effects of antiepileptic drugs. In: Shorvon S, Perucca E, Engel J Jr, eds. The treatment of epilepsy, 3rd edn. Oxford: Wiley-Blackwell, 2009: 289–300.

96 Messenheimer J, Mullens EL, Giorgi L, Young F. Safety review of adult clinical trial experience with lamotrigine. *Drug Saf* 1998; **18:** 281–96.

97 Patsalos PN, Berry DJ, Bourgeois BF, et al. Antiepileptic drugs: best practice guidelines for therapeutic drug monitoring—a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia* 2008; **49:** 1239–76.

98 Ruble J, Matsuo H. Anticonvulsant-induced cutaneous reactions: incidence, mechanism and management. *CNS Drugs* 1999; **12:** 215–36.

99 Hirsch LJ, Weintraub DB, Buchsbaum R, et al. Predictors of lamotrigine-associated rash. *Epilepsia* 2006; **47:** 318–22.

100 Simms KM, Kortepeter C, Avigan M. Lamotrigine and aseptic meningitis. *Neurology* 2012; **78:** 921–27.