Chapter 17

Side Effects of Antiepileptic Drugs

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Abstract

Adverse effects of antiepileptic drugs (AEDs) are common and result in treatment discontinuation in up to 25% of patients. The profile of adverse effects varies greatly among AEDs and markedly affects drug selection for individual patients. The most common adverse effects like cognitive impairment, coordination difficulties, and other CNS-related adverse effects are predictable, dose dependent, and reversible. They are of particular concern in patients who work or study. Idiosyncratic adverse reactions are unexpected events that cannot be explained by known mechanisms of action. Typically, they are not related to dose and they are associated with high risk of morbidity or even mortality. Some of them, like weight gain, can negatively affect treatment adherence. Many of AEDs increase the risk of congenital malformations or reproductive problems. New AEDs are usually better tolerated and some of them have no effect on hepatic drug-metabolizing enzymes which results in lower potential for drug interactions. Comparative, well-designed, and long-term trials are however needed to confirm better tolerability of the new AEDs and to assess their effect on quality of life, tolerability, and teratogenic potential.

Key words Epilepsy, Antiepileptic drugs, Side effects

1 Side Effects of Antiepileptic Drugs

Approximately 65 million people worldwide have epilepsy, making it the most common neurological disorder after stroke. Epilepsy is a multifactorial disorder that encompasses many seizure types and syndromes with different prognoses and sensitivities to available treatment. Treatment is symptomatic and limited to seizure suppression. Thus, current antiepileptic drugs (AEDs) are more accurately called "anti-seizure drugs" because they do not prevent or reverse pathological changes underlying development or progression of epilepsy and epilepsy-related comorbidities.

Adverse effects represent a leading cause of treatment failure, are a major impediment to optimal dosing for seizure control, and result in early treatment discontinuation in nearly 25% of patients. Adverse effects also negatively affect patient adherence to AEDs [1]. Furthermore, adverse effects are a major source of disability and mortality in patients with epilepsy and substantially contribute to the use

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and costs of healthcare systems. Recently, many new AEDs have been introduced into clinical practice. They have brought new therapeutic options, but their efficacy is not greater than that of old AEDs, and their use does not reduce the frequency of drug-resistant epilepsy in at-risk patients. Approximately 20–30% of patients continue to be pharmacoresistant with ongoing seizures, high risk of adverse effects, and considerable psychiatric comorbidities. In some patients, remission is achieved only at the expenses of serious side effects. In patients with epilepsy, drug treatment is usually necessary for several years, but it can last a lifetime. During such a long duration, various adverse effects of AEDs may appear and negatively affect the patient's quality of life. Systematic research and new methods of assessment of toxic effects may result in more effective strategies to detect and tackle the adverse effects of AEDs and to improve the quality of life for epileptic patients.

The frequency at which adverse effects are reported and, to a certain extent, their patterns are highly dependent on the method of their assessment. Particularly, studies on CNS effects often generate controversial data. Outcomes of these studies are affected by many variables; among them criteria used for selection of patients, length of therapy, and domains of measured effects play critical roles. The use of standardized and validated screening methods also helps to obtain comparable data and allows identification of populations at high risk for developing adverse effects.

It should also be stressed that an adverse effect is an unpleasant experience arising during drug exposure that is not necessarily caused by the drug. Thus, establishing causality can be challenging in uncontrolled studies and case reports, particularly when relevant information concerning dose, other treatments, or reversibility after discontinuation of therapy is missing (for a review, see reference [2]).

2 Definitions and Classification of Adverse Effects

The WHO's definition of an adverse drug reaction, which has been used since 1972, is *A response to a drug which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis*, *diagnosis*, *or therapy of disease or for the modifications of physiological function*. The term *adverse effect* encompasses all unwanted effects and is preferable to other terms such as *toxic effect* or *side effect*. A toxic effect is always dose related and occurs as an exaggerated therapeutic effect. On the other hand, a side effect is not associated with therapeutic effect and it may or may not be dose related [3]. Thus, the term "adverse effect" makes no assumption about mechanisms and avoids the risk of misclassification.

The term "adverse effect" must be distinguished from "adverse event." An adverse effect is an untoward experience that can be attributed to some action of a drug; an adverse event is an adverse outcome arising while the patient is taking a drug, but the event is not necessarily attributed to the drug [3].

Adverse drug effects can be classified by symptoms, severity, frequency, underlying mechanisms, or other parameters. According to the WHO, adverse drug reactions were originally divided into two basic groups, type A and type B. Type A is defined as "expected exaggerations of the drug's known effect that is usually dose dependent." Type B is "an idiosyncratic and unpredictable reaction, usually unrelated to the drug's known pharmacology." For the demands of modern pharmacology, two other categories were added to this classification, labeled type C (reaction related to the dose and time) and type D (delayed reaction). The latter classification was later split into withdrawal reaction (type E) and unexpected failure of therapy (type F) (for details, see reference [3]). Indeed, this classification, like others, has certain limitations because an adverse drug reaction can be difficult to classify into one of these categories. This classification was modified recently by Perucca and Gilliam [2] for AEDs (*see* Table 1).

Table 1

Modified classification of adverse effects according to Perucca and Gilliam (reference [2])

Type	Features	Example	Management
Type A	Related to known mechanisms of drug actions	CNS-related adverse effects (dizziness, somnolence, agitation)	Dose reduction or drug withdrawal, dosage modification
	Dose related		
	Common or very common, predictable		
	Low mortality		
Type B	Related to individual vulnerability (immunological, genetical)	Skin rash, hepatotoxic effects, pancreatitis, agranulocytosis, aplastic anemia	Immediate withdrawal, drug avoidance in future
	Not related to mechanism of action of the drug		Slow dose titration
	Not dose related		
	Unexpected, uncommon		
	High mortality		
Type C	Related to cumulative dose, occur after some time after the use of drug	Decreased bone density, endocrine effects, sexual and reproductive dysfunction, folate and vitamin D deficiency	Dose reduction or withdrawal, vitamin supplementation
	Time related		
	Uncommon, chronic, usually reversible		

(continued)

Table 1
(continued)

Type	Features	Example	Management
Type D	Teratogenic and carcinogenic effects Usually dose related Irreversible, delayed	Birth defects	Avoid drugs with known teratogenic effects in patients in risk (women with childbirth potential)
Type E	Adverse drug interactions Common, predictable	Increased risk of CNS neurotoxicity in combination of Na^{2+} blockers, decreased efficacy of warfarin in combination with carbamazepine, interaction between hormonal contraception and lamotrigine (reduced efficacy)	Avoid necessary polytherapy
Type F	Withdrawal related Usually related to abrupt withdrawal Uncommon	Status epilepticus, insomnia, agitation, psychiatric withdrawal symptoms	Slow withdrawal

3 Type A Effects

Type A adverse effects are defined as common, predictable, and related to a known pharmacological action of the drug. They are dose dependent, and they usually appear at the beginning of therapy or after dose escalation. The CNS effects are the most frequently reported type A adverse effects of AEDs and typically include fatigue, drowsiness, dizziness, coordination problems, concentration difficulties, memory problems, and irritability. Although the profile of CNS adverse effects varies from one drug to another, nearly all AEDs induce sedation and coordination disturbances to some extent (for a review, see reference [2]). Cognitive adverse effects observed as a result of AEDs are usually fairly modest, but can nevertheless be clinically significant because patients with even subtle adverse CNS symptoms display significant worsening of perceived quality of life [4]. Furthermore, cognitive and behavioral deficits are highly individualized and must be considered independently in every patient. Polytherapy or elevated plasma levels of AEDs increase the risk of CNS adverse effects.

In addition to AED effects, seizure etiology, and frequency, age of epilepsy onset and cerebral lesions also contribute to

cognitive functions in patients with epilepsy. It should be emphasized that epilepsy patients, as a group, have been shown to perform more poorly on a variety of cognitive measures compared to healthy controls.

As documented by many reports, AEDs exhibit a whole spectrum of CNS effects, not all of which are only negative with unfavorable impact on quality of patient's life. Some AEDs have beneficial effects on mood and behavior, and many AEDs are also used in psychiatry in non-epileptic patients. Available data from patients with epilepsy, however, demonstrate substantial differences in the CNS response to individual AEDs. For example, beneficial behavioral and mood-stabilizing effects of lamotrigine have been documented in many studies, whereas other studies report the development of psychosis in patients treated with lamotrigine. Such controversial data suggest that the behavioral response to AEDs in individual patients cannot be simply predicted only on the basis of a known mechanism of drug action.

In 1999, Ketter and collaborators [5] divided AEDs on the basis of their predominant psychotropic profiles into two global categories. One group of AEDs, acting predominantly through potentiation of inhibitory gamma-aminobutyric acid (GABA) neurotransmission, is assumed to have "sedating" effects in association with fatigue, cognitive slowing, and possible anxiolytic and antimanic effects. This group involves drugs such as barbiturates, benzodiazepines, valproate, gabapentin, tiagabine, and vigabatrin. The other group involves felbamate and lamotrigine and attenuates excitatory glutamate neurotransmission. These drugs are expected to be "activating," possibly with anxiogenic and antidepressant effects. AEDs with mixed GABAergic and antiglutamatergic actions may have "mixed" profiles. More recent analysis of available literature, however, did not bring conclusive evidence for this hypothesis (for a review, see reference [6]). Thus, in addition to mechanisms of action (*see* Table 2), there are other variables that play a role in the behavioral and mood-modifying effects of AEDs. Among these variables, age, the presence or absence of brain lesions, and the baseline mood state have to be considered in particular. Additionally, the extreme *age groups*, children and elderly patients, appear to be particularly sensitive to the cognitive or mood effects of AEDs. Immaturity of the nervous system in children may be responsible for the paradoxical responses described after administration of some AEDs, and several reports have indicated some differences in the mood effects of phenobarbital, carbamazepine, phenytoin, and valproate in pediatric populations. In particular, children on phenobarbital demonstrated poorer performance than children treated with valproate. Unlike in adults, administration of both phenobarbital and benzodiazepines in children often produces an acute reaction that includes hyperactivity, irritability, or aggression. Additionally, animal studies

Table 2

Main mechanisms of action of AEDs

Drug	Main mechanism of action
Phenobarbital	Enhancement of GABA-meditated inhibition
Phenytoin	Na^+ channel blocker
Primidone	Enhancement of GABA-meditated inhibition
Ethosuximide	Blockade of T-type of Ca^{2+} channel
Benzodiazepine	Enhancement of GABA-meditated inhibition
Carbamazepine	Na^+ channel blocker
Valproate	Multiple (enhancement of GABA-meditated inhibition, glutamate (NMDA) inhibition, Na^+ channel, and T-type calcium channel blockade)
Vigabatrin	Enhancement of GABA-meditated inhibition
Lamotrigine	Na^+ channel blocker, attenuation of excitatory transmission
Oxcarbazepine	Na^+ channel blocker
Gabapentin	Blockade of α2δ subunit of Ca^{2+} channel, effects on GABA turnover
Tiagabine	Enhancement of GABA-meditated inhibition, inhibition of glial GAT-1
Topiramate	Multiple (GABA potentiation, AMPA inhibition, Na^+ and Ca^{2+} channel blockade)
Levetiracetam	SV2A modulation
Zonisamide	Na^+ and T-type Ca^{2+} channel blocker, carbonic anhydrase inhibition
Stiripentol	Enhancement of GABA-meditated inhibition, Na^+ channel blocker
Pregabalin	Blockade of α2δ subunit of Ca^{2+} channel
Rufinamide	Na^+ channel blocker
Lacosamide	Enhancement of slow inactivation of voltage-gated Na^+ channel
Eslicarbazepine acetate	Na^+ channel blocker
Perampanel	Glutamate (AMPA-Rp) antagonist

This table summarizes the predominant mechanisms of action for each AED. It is, however, important to realize that only a limited number of AEDs (ethosuximide) are characterized by a single mechanism of action. In fact most of AEDs have multiple mechanisms of action

have suggested that children may be at increased risk for enduring cognitive impairment because of the possible interference of the AEDs with normal development. In elderly patients, the increased risk of adverse cognitive effects is usually associated with age-related changes in pharmacokinetics.

Mood and anxiety disorders represent the most frequently reported psychiatric problems in patients with epilepsy, and both

biological and psychological reasons were identified [7]. Biological contributors involve neuroanatomical factors, including involvement of temporal lobe structures, severity and distribution of brain lesions, and various epigenetic changes at molecular, cellular, and structural levels. Such changes may both lead to rebuilding of the brain circuitry and participate in functional alterations occurring in epilepsy patients. In addition, epilepsy is a chronic, stigmatizing disorder that brings various social limitations that can contribute to development of psychiatric problems. Seizure reduction with related improvement in quality of life can positively affect the patient's mood. On the other hand, in people with learning disabilities associated with ongoing seizures, sudden seizure control can result in "release phenomenon" because the patient did not have chance to develop proper skills in how to use their new-found abilities. Similarly, patients who are not able to express their concerns about adverse effects in words can instead react aggressively. Such behavioral disturbances are not direct effects of the drug, but they have yet to be well identified in order to be eliminated (for a review, see reference [8]).

Apparently, proper assessment of both beneficial and adverse CNS effects is of high clinical relevance, and the selection of optimal AEDs can help not only to manage seizures but also to reduce psychiatric problems accompanying epilepsy. However, improper selection of AEDs or their combinations can cause mood-related problems and result in severe behavioral disturbances. The following part of this review therefore not only summarizes the adverse effects of AEDs but also presents brief insight into possible beneficial CNS effects of these drugs.

4 Old Antiepileptic Drugs

Phenytoin, primidone, phenobarbital, carbamazepine, valproate, ethosuximide, and benzodiazepines have been used in monotherapy or polytherapy for many years, and their adverse effects are relatively well established. Mood effects of these drugs are usually moderate and can be clinically significant. Typically, they include sedative effects and coordination disturbances such as vertigo, imbalance, ataxia, nystagmus, or diplopia. For *phenytoin*, agitation, increased anxiety, and alterations of emotional state have been reported, however, only after high doses [9, 10]. *Phenobarbital*, like other barbiturates and *benzodiazepines*, has sedative effects in adults, whereas it often induces hyperactivity in children with epilepsy. Both *phenobarbital* and *benzodiazepines* have the most detrimental effects on cognition.

Consistent with the structurally similar tricyclic antidepressants, *carbamazepine* is used in psychiatry for the treatment of mood disorders, primarily mania and rapid cycling bipolar disorders, depression, and dysphoria and with some limitation for

bipolar and unipolar depression and dysphoria (for a review, see reference [11]). Carbamazepine may help control agitated or disruptive behaviors, viewed dimensionally across a spectrum of psychiatric disorders, including attention deficit/hyperactivity, intermittent explosive behavior, post-traumatic stress, and personality disorders, as well as in mental retardation, dementia, and alcohol and possibly benzodiazepine withdrawal. Fenwick [12] characterized carbamazepine as a mood-stabilizing drug. However, data regarding carbamazepine therapy and psychosis in patients with epilepsy are controversial. A double-blind study with adjunctive carbamazepine revealed improvement in chronically psychotic psychiatric patients with temporal lobe epilepsy [13]. In contrast, no studies have documented serious mood effects. There are studies reporting occasional development of acute psychosis in some epilepsy patients receiving carbamazepine, but these studies are usually case reports. The effects of carbamazepine on cognition are relatively mild, and only a few cognitive differences between carbamazepine, phenytoin, phenobarbital, or primidone were reported in a large group of new-onset epilepsy patients who were followed for at least 36 months [14]. In a more recent study, Keene et al. [15] did not find any differences in cognitive side effects between add-on therapies with carbamazepine, phenytoin, and clobazam in children with refractory epilepsy.

Valproate, a drug with multiple mechanisms of action, may relieve mood symptoms and agitation in epilepsy patients [16]. Epilepsy patients with concomitant neurological problems (abnormal EEG, head injury) had better rates of affective improvement than patients without neurological abnormalities [16]. Valproate rarely causes somnolence, fatigue, and mild cognitive impairment [17].

Contradictory effects of valproate on mood function have been reported in pediatric patients. In some studies, no behavioral effects were found [18], whereas in children with behavioral problems, mental retardation and hyperactivity were reported [19, 20]. However, Herranz and collaborators [21] reported behavioral effects of valproate in 65 % of children on valproate monotherapy. In a minority of these children, sedating effects were observed, while most showed increased irritability or hyperactivity. Similarly, like in adults, valproate seems to be more beneficial in children with a "mood-activated" profile, while valproate may lead to behavioral disturbances in children without baseline problems [6].

There is limited information concerning the mood and behavioral effects of *ethosuximide*. Dizziness, fatigue, and somnolence represent the most frequently reported CNS adverse effects observed in patients treated with ethosuximide (for a review, see reference [22]). A controlled study did not find any mood effects of ethosuximide or its association with cognitive impairment [23].

5 New Antiepileptic Drugs

As mentioned above, the new AEDs are expected to be better tolerated and to affect cognitive functions to a lesser extent than the old AEDs. Although most of the previous studies dealt with the putative advantages of newer over older AEDs, some serious adverse CNS effects are observed after their administration.

Similarly, sedative effects and coordination disturbances of old AEDs represent the most commonly reported CNS-related adverse effects of new AEDs although sedative effects are more frequent and severe with the old AEDs: benzodiazepines, phenobarbital and primidone [2]; however, coordination problems were documented in all third-generation AEDs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, retigabine, tiagabine, topiramate, zonisamide) [24, 25].

Because of fatal adverse hematological and hepatological effects, *felbamate* is currently used only in severe refractory forms of epilepsy such as the Lennox-Gastaut syndrome. Felbamate is an NMDA receptor antagonist, and at the same time, it potentiates GABA-mediated events. In children, somnolence, insomnia, and anorexia are the most frequently reported CNS effects. A similar profile including diplopia and headache was also reported in adults [26]. Adverse psychiatric effects are consistent with the activating profile of felbamate and include anxiety, manic depression, irritability, aggression, mania, and psychosis [27, 28]. Patients with previous psychiatric problems may or may not be at increased risk of aggravation of psychiatric problems. Favorable behavioral effects of felbamate were reported in patients with Lennox-Gastaut syndrome. Gay et al. [29] documented significant improvement in social, intellectual, and motor functioning and improvement of attention, concentration, and memory.

Mechanism of action for *gabapentin* is not fully understood, but it binds to the Ca^{2+} channel α2δ subunit. It also affects GABA turnover. Clinical studies documented rather positive mood effects of gabapentin, including decreased anxiety and depression or mood stabilization [30]. In epilepsy patients, gabapentin is generally well tolerated despite some sedative effects [31]. In adult patients, development of psychosis or depression was reported only sporadically [32]. Reports from pediatric patients are controversial. Some studies have documented behavioral disturbances including hyperactivity, irritability, and agitation in children with add-on gabapentin [33, 34]. The risk of developing these behavioral disturbances was higher in children with preexisting attention deficits and other behavioral problems. In contrast, Besag [35] did not report frequent or serious behavioral disturbances in children or teenagers with learning difficulties after gabapentin was added to their current therapy.

The positive mood effects of gabapentin were also reported in patients with epilepsy. Almost 50% of patients reported improvement in general well-being compared to those with placebo [36]. Effects of gabapentin on cognitive performance are less adverse than those of carbamazepine [37]. Additionally, the risk of developing depression is low (for a review, see reference [38]).

There are many reports on the beneficial behavioral effects of *lamotrigine* in patients with epilepsy, in particular on bipolar mood disorders and depression (for a review, see reference [8]). Lamotrigine is a Na^+ channel blocker, but it was also found to attenuate glutamate release. Lamotrigine-treated patients not only performed better in 48% of neuropsychological measures compared with those on carbamazepine but also scored better on measures of memory, attention, and a number of quality-of-life measures [39]. As documented by a multicenter international trial, a majority of children and adolescents on lamotrigine improved on global assessments [40], and significant behavioral improvement was also observed. In a double-blind, placebo-controlled study, *lamotrigine* was not associated with any cognitive impairment [41], and multiple studies comparing lamotrigine with other AEDs reported fewer adverse cognitive effects. Although adjunctive lamotrigine induces more somnolence than placebo, sedative effects are less common than with carbamazepine [42]. Placebo-controlled trials have shown low rates of psychosis and depression in patients taking lamotrigine (>1%; for a review, see reference [38]). Mood improvements have been reported in several open clinical studies in both adults and children taking lamotrigine [42–44]. There are only a few case reports of psychosis attributed to lamotrigine treatment. The development of psychosis was documented in both adult and pediatric patients receiving lamotrigine as add-on therapy (for a review, see reference [8]).

Levetiracetam possesses a unique pharmacological activity profile; it binds selectively to the synaptic vesicle protein, SV2A, which is involved in the exocytosis of neurotransmitters [45]. The most commonly reported CNS adverse effects of levetiracetam include somnolence, dizziness, irritability, and behavioral disturbances, but their incidence is relatively low [31]. The most severe adverse effects, such as psychosis, are most common in patients with a previous history of psychotic diseases [46]. Similar to felbamate and tiagabine, levetiracetam presents an intermediate risk of depression (4%). A more recent study with add-on levetiracetam in children and young adults [47] is in line with previously published data confirming the safety of this drug.

Topiramate is a drug with multiple mechanisms of action that involve GABA potentiation, AMPA inhibition, and Na^+- and Ca^{2+}-channel blockade, suggesting that it might have beneficial effects in some patients and detrimental effects in others. In older literature, the use of topiramate was associated with a relatively high risk

of developing neurocognitive and behavioral problems compared to newer AEDs (lamotrigine, gabapentin, vigabatrin) [48]. An audit of topiramate, carried out by Crawford [32], determined a risk of psychotic syndromes at 12%. A slow titration schedule, however, is associated with lower prevalence of psychiatric adverse effects. Another relevant risk factor is having a history of psychiatric disorders [49]. Beneficial behavioral effects of topiramate in patients with mood disorders were reported by Marcotte [50], who found improvement in 52% percent of patients with bipolar affective disorders.

Tiagabine inhibits reuptake of GABA. This drug is associated with a relatively high risk of coordination problems, somnolence, and dizziness, as reported in up to 22% of patients [51]. Incidence of serious psychiatric adverse events such as psychosis is not significantly higher than those with placebo [52]. According to individual studies, risk of depressed mood ranges between 1% [53] and 5% [54]. Some studies suggested beneficial effects of tiagabine in patients with mania, but data are limited (for a review, see reference [8]).

Because peripheral vision constriction occurs in up to 40% of patients [55], the use of *vigabatrin* is limited only to situations when it is absolutely necessary. Major CNS adverse effects of vigabatrin, which acts as a suicide inhibitor of GABA transaminase, include dizziness, fatigue, and drowsiness. Its administration is associated with increased risk of behavioral disturbances, ranging from irritation to psychosis. Patients with a previous history of psychosis are at increased risk of psychotic symptoms [56]. It is of interest that vigabatrin seems to be better tolerated in pediatric patients, and psychotic reactions have rarely been reported in children [57]. Review of data from double-blind, placebo-controlled studies revealed increased incidence of depression in patients treated with vigabatrin [58]. Treatment with this drug did not produce significant cognitive deterioration and had no effects on the quality-of-life measures [59].

The most common CNS adverse effects of *oxcarbazepine* are similar to those of carbamazepine. Behavioral disturbances are not usually reported. Oxcarbazepine is generally well tolerated and rather beneficial compared with the adverse CNS effects that have been reported (for a review, see reference [8]).

Zonisamide acts through multiple mechanisms of action. It blocks sodium and T-type calcium channels and inhibits carbonic anhydrase. The most frequently reported CNS adverse events are agitation and irritability, with higher incidence compared to placebo (data from manufacturer). Frequency of psychosis with zonisamide was similar to that reported with other AEDs. Incidence of depression was higher than in placebo, but this effect is likely dose dependent, and its risk increases with used dose. Compared to placebo, somnolence, anorexia, and ataxia were slightly more common with zonisamide treatment [60–62].

Data concerning adverse CNS effects of the newest AEDs are still limited, but in general, adverse CNS effects were reported in all of them. Meta-analysis of double-blind studies on neurological adverse events of new-generation sodium blockers, *eslicarbazepine acetate*, *lacosamide*, and *oxcarbazepine*, demonstrates increased risk of dizziness, diplopia, vertigo, or coordination problems compared to placebo. These effects were more frequently observed after oxcarbazepine than after eslicarbazepine acetate or lacosamide [63]. Similar to gabapentin, *pregabalin* interacts with calcium ion channels and increases the level of GABA in neuronal tissue. It is well tolerated, causing dizziness, somnolence, and ataxia of only mild to moderate intensity [64]. Similar adverse CNS effects were reported in patients treated with *perampanel*, a new AMPA glutamate receptor antagonist, and *retigabine*, acting primarily through the opening of voltage-gated KCNQ2/3 potassium channels. Both drugs have also demonstrated the ability to induce neuropsychiatric symptoms [65].

The renal adverse effects of AEDs are dependent on the mechanism of action. The risk of kidney stones is associated with the AED's potential to inhibit carbonic anhydrase. The development of calcium phosphate kidney stones was reported in approximately 1% of patients treated with *topiramate*, *zonisamide*, and *acetazolamide*. The risk increases with dose and treatment duration [66–68]. Due to its direct effects on the smooth muscles of the bladder, administration of *retigabine* in higher doses is associated with approximately 10% risk of urinary retention [69].

6 Type B Effects

Type B or idiosyncratic adverse reactions refer to unexpected events that cannot be explained by known mechanisms of action and occur unpredictably in susceptible individuals. Typically, they are not related to dose. Individual susceptibility can be due to immunologic, genetic, or other mechanisms. Type B adverse events are less common than type A effects. They usually arise shortly after the therapy onset, and they can be reversed after drug withdrawal. Type B effects are associated with high risk of morbidity or even mortality.

The most common types of idiosyncratic reaction to AEDs include cutaneous, hematological, hepatic, and pancreatic responses (for a review, see reference [70]). Skin rash occurs in approximately 5–17% of patients on *lamotrigine*, *phenytoin*, *carbamazepine*, and *phenobarbital* (for more details, see reference [71]). Stevens-Johnson syndrome or toxic epidermal necrolysis affects 1–10 of 10,000 new users of these AEDs [72]. Known risk factors for cutaneous adverse reactions are high starting dose and rapid dose escalation, history of immune system disorders, and age. For example, lamotrigine-induced serious and benign skin rashes occur more frequently in children than in adults, probably because of

age-related differences in drug metabolism [70]. Additionally, pharmacogenetics may be helpful in selecting patients with increased risk of serious dermatologic hypersensitivity reaction. In Asia, the presence of human leukocyte antigen HLA-B*1502 is highly associated with Stevens-Johnson syndrome induced with carbamazepine and probably also with phenytoin, lamotrigine, and oxcarbazepine [73]. Among others, HLA genes and the antigen HLA-A*3101 are associated with carbamazepine-induced cutaneous reactions. However, this association was found in more diverse ethnic groups (for a review, see reference [71]).

AEDs are among the drugs that most frequently cause liver necrosis leading to transplantation, and hepatotoxic effects of AEDs can occur in isolation or as a part of DRESS (drug rash with eosinophilia and systemic symptoms). *Valproate*, *phenytoin*, and *felbamate* carry the highest risk of hepatic failure. Transient elevation in liver function tests appears in 15–30% of patients with valproate [74]. Valproate and phenytoin were responsible for drug-induced acute hepatic failure leading to liver transplant in 7.3% of patients. Pediatric patients are at greater risk and valproate-induced hepatotoxicity occurs in one in 500–800 cases in young children under the age of 2 years receiving valproate polypharmacy [75]. For felbamate, the risk for hepatic failure is estimated at one per 18,500–25,000 exposures (for a review, see reference [76]).

Several AEDs can induce life-threatening hematological adverse effects. In general, exposure to AEDs excluding patients on felbamate is associated with a nine times higher risk of developing aplastic anemia [77]. *Felbamate* is associated with the greatest risk of fatal aplastic anemia with an incidence of 127 per one million [78]. Risk of developing aplastic anemia in patients with felbamate is up to 20 times higher than in those with carbamazepine. Predictors of felbamate-induced aplastic anemia include immune diseases, especially lupus erythematosus, allergy, and prior cytopenia (for a review, see reference [76]). *Carbamazepine* has the highest potential for causing agranulocytosis [79].

7 Type C Effects

Chronic adverse effects are those that manifest after a prolonged period of exposure lasting from months to years. They progress slowly and although some of these effects are reversible, others can be irreversible. Most serious adverse effects belonging to this group are associated with exposure to enzyme-inducing AEDs. Among the most important adverse effects, type C effects are reproductive disorders in man, abnormalities in bone health, cardiovascular problems, and weight gain.

Long-term treatment with AEDs can cause decreased bone mineral density and increased risk of fractures. A study by Pack

[80] revealed that epilepsy patients have a greater risk of fracture than the general population, and osteopenia or osteoporosis was detected in 38–60% people with epilepsy (for a review, see reference [81]). The risk is particularly high in enzyme-inducing drug exposure. Changes seen after exposure to these drugs are related to their hepatic enzyme inducting properties which are responsible for accelerated degradation of vitamin D. Negative effects on bone mineral density are associated primarily with administration of phenobarbital and phenytoin. Valproate and carbamazepine can also have negative impacts on bone health, but data are inconsistent (for a review, see reference [82]).

AED therapy is often associated with endocrine adverse effects. Sexual dysfunctions, reproductive disorders, and changes in hormone levels represent common problems among epileptic patients. The most robust effects on sexual hormone levels were reported in patients treated with enzyme-inducing AEDs primarily with *phenytoin* and *carbamazepine*. Enzyme-inducing AED exposure is associated with acceleration of the breakdown and production of sex hormone-binding globulin (SHBG). This results in increased SHBG and reduced levels of biologically active estrogen and androsterone. Additionally, reduced levels of serum dehydroepiandrosterone sulfate (DHAES) have been reported in men and women taking *phenytoin* and *carbamazepine* (for a review, see reference [83]). *Valproate* does not induce liver enzymes, but it does reduce serum gonadotropin levels, probably through direct central effects [84]. In addition, valproate, but not carbamazepine, was found to affect semen morphology and motility [85]. In women with epilepsy, administration of valproate is associated with the highest risk of endocrine and reproductive problems. These women have significantly more menstrual disorders than controls, and these were frequently associated with polycystic ovary syndrome and/or hyperandrogenism, which were detected in 70% of women receiving valproate, 20% of *carbamazepine*-treated women, and 19% of women acting as controls [86]. In addition, results of several studies in pubescent girls treated with valproate indicate that young ovaries are more susceptible to long-lasting endocrine changes (for a review, see reference [83]). *Lamotrigine* and *levetiracetam* were not found to cause endocrine disturbances or reproductive problems, but data on levetiracetam are still inconclusive [84]. There is growing evidence that *topiramate* administration can cause sexual dysfunction. Data concerning other newer AEDs are sparse and randomized studies are still lacking (for a review, see reference [83]).

In addition to effects on sexual hormones, some AEDs can also affect thyroid function. In spite of their clinical importance, these adverse effects are only rarely mentioned. Significant alteration of thyroid functions has been reported in patients treated long-term with *carbamazepine oxcarbazepine* and *phenytoin*, but not with valproate [87, 88].

Changes in bodyweight represent another typical type C effect of AEDs. Weight gain is typically reported in patients treated with valproate, gabapentin, pregabalin, vigabatrin, retigabine, and, to a lesser extent, carbamazepine. Weight gain poses a serious health hazard and carries an increased risk of hypertension, type 2 diabetes mellitus, and dyslipidemia [89]. It also increases risk of non-adherence or discontinuation of treatment. In contrast, topiramate, zonisamide, felbamate, stiripentol, and rufinamide can cause weight loss, which is potentially beneficial in overweight or obese individuals [90].

Vigabatrin-induced restriction of the bilateral visual field is another serious type C adverse effect of AEDs. Loss of the visual field is irreversible and was reported in 44% of adult and 34% of pediatric patients. Risk factors involve cumulative dose and increasing age (for a review, see reference [91]).

8 Type D Effects

Through clinical experience and pregnancy registries, it is known that children of women with epilepsy are at increased risk of congenital defects and neurodevelopmental deficits. While a variety of problems can contribute to neurodevelopmental problems in children of women with epilepsy, AEDs appear to play a major role. Possible teratogenic effects of AEDs are a major concern in women of childbearing potential treated for epilepsy. In addition to increased risk of serious birth defects, the risk for mental retardation related to intrauterine growth retardation, reduced head circumference, and other factors was also reported (for a review, see reference [92]). A relatively high risk of congenital malformations and neurodevelopmental problems are associated with exposure to old, enzyme-inducing AEDs. Their teratogenic potential is determined by the chemical attributes of the AEDs and also by the genetic attributes of the patient. Drug metabolism plays a critical role in teratogenesis because not only maternal compounds but also intermediate, active metabolites can be responsible for teratogenic effects. For example, drugs containing an aromatic ring, such as carbamazepine or lamotrigine, are converted to a reactive epoxide or arene oxide that can interact with macromolecules to produce toxicity (for a review, see reference [93]).

Risk of congenital malformations varies across AEDs, with *valproate* and *phenytoin* carrying a higher risk than carbamazepine, phenobarbital, and lamotrigine. According to the most recent data from the Australian Pregnancy register [94], valproate monotherapy is associated with a five- or sixfold risk of fetal malformation and carbamazepine monotherapy with a little over twofold increase relative to that in pregnancy not exposed to AED. Exposure to lamotrigine in monotherapy was not associated with a significantly higher risk of malformations than other newer AEDs taken as monotherapy. Polytherapy carries increased risk of birth defects especially when valproate is used.

In addition to increased risk of fetal malformations, many studies also report neurodevelopmental deficits in children of mothers with epilepsy suggesting behavioral teratogenicity of AEDs (for a review, see reference [92]). Most frequently, cognitive impairment, learning difficulties or behavioral impairment are mentioned, but methodological differences and variability in patient populations are probably responsible for inconsistencies among the data. Additionally, there are many other variables that can influence the neurodevelopmental outcome of children born to epileptic mothers such as generalized tonic-clonic seizures or genetic factors (for a review, see reference [95]). However, it is apparent that not all AEDs are the same with regard to behavioral teratogenicity. The highest risk of unfavorable neurodevelopmental outcome is associated with fetal exposure to *valproate*. The prospective NEAD study demonstrated significantly lower IQ in children exposed to *valproate* in utero compared to those exposed to phenytoin, lamotrigine, or carbamazepine. Association between IQ and valproate was dose dependent [96–98]. Poor cognitive outcome was also reported in children exposed to *phenobarbital* and exposure involving the last trimester was the most detrimental [99]. Although risk appears to be lower than with valproate, cognitive deficits were also reported in children exposed to *phenytoin* [100]. Whereas the data are contradictory, exposure to carbamazepine or lamotrigine appears to confer only a low risk of neurodevelopmental problems.

9 Type E Effects

Adverse reactions due to drug interactions in epilepsy patients are relatively common and usually clinically important. Most AEDs affect the activity of drug-metabolizing enzymes or are substrates for the same enzymes; therefore, pharmacokinetic drug interactions are particularly important. Pharmacokinetics concern processes related to drug absorption, distribution, metabolism, and elimination from the body. Consequently, interactions can occur at all of these levels. If the drug has pharmacologically active metabolites, then interaction may involve both the parent drug and these metabolites.

Drug interactions associated with distribution closely relate to the degrees of their binding to blood albumins. Any interactions are likely to occur when at least 90% of drug is protein bound. *Phenytoin*, *valproate*, and *tiagabine* fulfill this criterion, whereas *gabapentin*, *pregabalin*, *vigabatrin*, and *ethosuximide* are not considerably protein bound [101, 102]. Displacement of the drug from the protein-bound state may lead to an increase in its free plasma levels. Because many AEDs have a narrow therapeutic index, increased levels of free drug can increase the risk of toxic effects.

Metabolic interactions most frequently occur at the level of cytochrome P-450 (CYP) or UDP-glucuronosyltransferase (UGT).

The CYP pathway is involved in the metabolism of first-generation AEDs such as *carbamazepine*, *phenobarbital*, *primidone*, and *phenytoin*. Among newer AEDs, the CYP pathway plays an important role in the metabolism of *felbamate*, *topiramate*, *tiagabine*, and *zonisamide*. The UGT pathway metabolizes *lamotrigine* and *valproate*. *Carbamazepine*, *phenobarbital*, *primidone*, and *phenytoin* are typical enzyme inductors, and they act as metabolic activators. They reduce the serum concentration and efficacy of a wide range of medications, including cardiovascular, psychotropic, antimicrobial, and antineoplastic drugs, as well as oral contraceptives or immunosuppressants. For example, carbamazepine enhances the metabolism of warfarin [103]. On the other hand, some drugs, such as *valproate*, act as CYP inhibitors. They may cause an increase in plasma levels of parent drugs or their toxic metabolites and consequently enhance the risk of toxic effects. Concomitant administration of valproate and carbamazepine increases serum level of carbamazepine-10,11-epoxide, an active carbamazepine metabolite, which is responsible for most of its serious toxic effects (for a review, see reference [103]).

With regard to the UGT pathway, *oxcarbazepine* is a UGT activator that accelerates metabolism of lamotrigine. On the other hand, *valproate* is a UGT inhibitor, and it may affect the metabolism of lamotrigine (for a review, see reference [103]). Although most of the newer AEDs have a significantly reduced potential for drug interactions, they are not free of type E adverse effects. Importantly, *oxcarbazepine*, *lamotrigine*, *felbamate*, *topiramate*, and *rufinamide* can reduce serum levels of oral contraceptives [104].

Interactions at the level of renal excretion are unlikely to happen among AEDs; however, interactions with other drugs excreted in the same way cannot be excluded (for a review, see reference [103]).

Pharmacodynamic interactions at the site of action have also to be considered in epilepsy treatment. In contrast to pharmacokinetic interactions, pharmacodynamics interactions are not associated with changes in the serum or brain levels of combined drugs. Pharmacodynamic interactions assume summation or even potentiation of drug receptor or non-receptor effects (for a review, see reference [102]). In particular, co-prescription of AEDs with the same mechanisms of action can lead to summation/potentiation of their neurotoxic effects (for a review, see reference [105]).

10 Type F Effects

Despite its benefits, stopping AEDs in seizure-free patients is associated with the increased risk of seizure recurrence for up to 2 years compared with continued treatment. Furthermore, the outcome of treating a seizure recurrence in patients who have been seizure-free for years may be surprisingly poor (for a review, see reference

[106]). However, patients chronically treated with AEDs are at risk of serious adverse effects, including possible teratogenic effects (for a review, see reference [107]).

Abrupt discontinuation of AEDs carries a particularly high risk of serious withdrawal reaction frequently involving frequent seizures, status epilepticus, and psychiatric withdrawal symptoms. Antiepileptic drug non-adherence is a common cause of SE across all ages, particularly in children and adolescents. Prompt and reliable recognition of non-adherence is imperative for correct management (Lie et al. [108]).

11 Conclusion

The long-term safety of AEDs primarily depends on their systemic and metabolic effects and on the genetic predisposition of the host. Adverse effects of AEDs are common, frequently contributing to treatment failure. They have also emerged as one of the strongest predictors of impaired quality of life, independent of seizures. However, the majority of adverse effects of AEDs are predictable. Patient education can therefore substantially decrease the risk of developing long-term, serious adverse events. Overtreatment should be avoided to minimize risk of dose-dependent adverse effects. Pharmacoepidemiological resources can help to identify the individual profiles of patients at high risk of specific adverse effects. Additionally, the successes in pharmacogenomics may help to select patients with increased risk of serious, life-threatening toxic effects such as Stevens-Johnson syndrome of toxic epidermal necrolysis. In addition, assessment of potential risks should include age, sex, childbearing potential, and presence of somatic and psychiatric comorbidities. Introduction of new AEDs with new mechanisms of action provides better opportunities for individually tailored pharmacotherapy for each patient to maximize efficacy and to minimize the risk of adverse events. New-generation AEDs are not free of adverse effects, although they typically have better tolerability and reduced potential for drug interactions.

Despite progress made in the safety of AEDs, new AEDs with fewer adverse effects and better efficacy than the currently available drugs are still needed. Treatment that would prevent or favorably modify processes leading to the development of epilepsy in patients with a known risk due to genetic predisposition or brain injury is an unmet need in epileptology.

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