Adverse motor effects induced by antiepileptic drugs

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ABSTRACT – Cognitive effects of anti-epileptic drugs (AEDs) have been already extensively reported. In contrast, motor disturbances, frequently induced by these drugs, have not received similar attention. We review subjective and objective adverse motor effects of traditional and new AEDs. We discuss the methodological issues caused by the heterogeneous sources of information on drug adverse effects (controlled clinical studies, open studies, and case reports). We describe specific disturbances (vestibulocerebellar, dyskinesias, parkinsonism, tics, myoclonus, and tremor) as the effects of different AEDs on distinct motor circuitries. Finally, we summarize the role of sophisticated technical studies which provide a valuable insight into the specific or subtle effects of AEDs on the central nervous system.

KEY WORDS: antiepileptic drugs, adverse effects, ataxia, diplopia, dyskinesias, movement disorders, myoclonus, parkinsonism-tremor

Adverse drug reactions may be directly related to the primary and/or secondary pharmacological effects of a drug (Type A). Such effects are usually predictable, dose-dependent and resolve with dose reduction. In other cases, adverse events are host-dependent and are not characterized by a simple dose-response relationship (idiosyncratic or Type B). Finally, adverse effects can be caused by cumulative effects of long-term therapy (Type C) [1].

As anti-epileptic drugs (AEDs) mainly exert their pharmacodynamic properties at the central nervous system (CNS) level, the most frequent AED-induced adverse effects affect the CNS itself. These effects are usually type A, although idiosyncratic reactions have been also reported (e.g. hyperammonaemic encephalopathies induced by valproic acid [2, 3, 4]).

Recently, new AEDs have modified the landscape of epilepsy treatment. Several valuable reviews address the adverse effects of AEDs [5, 6, 7]. Also, cognitive effects of old and new AEDs have been extensively reviewed [8, 9, 10, 11, 12]. In contrast, motor effects induced by AEDs have not received similar attention even though they are common. In an epidemiological study, 144 out of the 232 AED-induced adverse reactions (62%) involved the CNS [13], and 62 patients complained of adverse motor effects, including nystagmus, ataxia, vertigo, tremor and diplopia. Moreover, in a recent metanalysis, Cramer et al. [14] reported that the adverse effects of new AEDs affected motor performances more frequently than other CNS functions.

Adverse motor effects of a given drug can be subjective (symptoms) and objective (signs). Signs can be both motor deficits or involuntary movements. In the present paper, we review the available data on the adverse effects of AEDs on motor systems. Dizziness has been included in the motor symptoms as it reflects vestibular impairment leading to postural instability.
Methodological problems

A computer-aided search of Medline (PubMed) was conducted for articles in the English language concerning humans from 1967 to April 2003. The literature database was acquired using the Boolean keyword strings: (adverse motor effects OR each single adverse motor effect) AND (antiepileptic drugs OR each single AED), with supplementation by relevant articles from reference list searches and chapters of books. More than 900 articles were found, and 219 of them, representing the major findings in this field, were selected and reviewed by one of the authors (GZ) and categorized according to study rationale. The overall process was confirmed by consultation between reviewers. Disagreements were resolved by discussion.

It has been observed that data concerning adverse drug effects come from different sources, such as controlled clinical trials, open studies, and case reports. In these studies, patients can be treated by mono- or polytherapy. The heterogeneity of this information causes several methodological issues. Placebo-controlled phase three studies could represent an optimal approach to analyse Type A adverse effects (which are frequent, dose-dependent and more often observed at the beginning of therapy). However, if the experimental drug is added to pharmacoresistant patients treated with high doses of standard AEDs, a given adverse event could depend on total drug load and/or on pharmacokinetic/pharmacodynamic interactions. For example, felbamate has stimulant-like proprieties if administered in monotherapy; however, a different profile of tolerability was observed when felbamate was administered with other ‘traditional’ AEDs, whose metabolism may be inhibited by this drug [15].

For ethical reasons, double-blind studies with a new AED versus placebo have been rarely performed in newly diagnosed epileptic patients [16]. As regards comparative monotherapy studies, sometimes a given drug-induced adverse effect (i.e. headache) cannot be separated from disturbances due to co-morbidity (i.e. migraine).

Case reports provide a detailed description of infrequent adverse events, although they cannot correctly estimate the prevalence of these effects since the population at risk is generally unknown. Finally, sophisticated technical studies may provide a valuable insight into specific or subtle effects of AEDs on the CNS in patients or in healthy controls. Each source of information provides a different picture, and this should be considered when we analyse data.

Another potential source of error is that objective, quantifiable measures of the adverse effects most frequently complained by patients have not been or cannot be used in clinical studies. In addition, heterogeneity of populations, terminology, methods for collecting adverse effects (e.g. check lists or spontaneous reporting), make comparison across studies very difficult [6].

In each section of this article, we will discuss a specific adverse motor system effect. In the first part of each section we have included traditional drugs [phenobarbital (PB), primidone (PRI), phenytoin (PHT), carbamazepine (CBZ) and valproic acid (VPA)]. Benzodiazepines will not be discussed. In the second part, we have included new AEDs [felbamate (FBM), gabapentin (GBP), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), tiagabine (TGB), topiramate (TPM), vigabatrin (GVG)].

Vestibulocerebellar and brain stem dysfunction

Many drugs may determine brainstem and/or cerebellar dysfunction [5, 7] resulting in disorders of upright stance and gait (ataxia, incoordination, dizziness, and vertigo), and ocular motricity (diplopia and oscillopsia).

Traditional drugs

Case reports and observational studies show that dose-related vestibulocerebellar dysfunction with ataxia and nystagmus is typically observed during acute PHT and CBZ toxicity [17, 18]. Nystagmus is usually the first sign of drug intoxication, whereas ataxia appears at higher dosages [19-21]. The clinical picture of overdose is characterised by non selective CNS involvement with mental changes and a variety of ophthalmological signs ranging from horizontal nystagmus to complete external ophthalmoplegia [22, 23] (See table 1). Barbiturates, particularly PB, have a different spectrum of neurotoxicity with sedation usually appearing as the first symptom [24]. Finally, of the traditional AEDs, VPA is considered to be the less effective on vestibulocerebellar structures [25].

In the ‘80s and in the first part of ‘90s, several clinical studies were performed to evaluate the frequency of adverse effects in populations of newly diagnosed adults [26-29] and paediatric [30, 31] patients taking different AEDs in monotherapy. In one study, PB was associated

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Description</th>
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<tbody>
<tr>
<td>carbamazepine (CBZ)</td>
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<tr>
<td>felbamate (FBM)</td>
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</tr>
<tr>
<td>gabapentin (GBP)</td>
<td></td>
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<tr>
<td>lamotrigine (LTG)</td>
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<td>levetiracetam (LEV)</td>
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<tr>
<td>oxcarbazepine (OXC)</td>
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<tr>
<td>phenobarbital (PB)</td>
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<tr>
<td>phenytoin (PHT)</td>
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<tr>
<td>primidone (PRI)</td>
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<tr>
<td>tiagabine (TGB)</td>
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<td>topiramate (TPM)</td>
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<tr>
<td>valproic acid (VPA)</td>
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<td>vigabatrin (GVG)</td>
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with the lowest incidence of motor disturbances compared to PRI, PHT and CBZ [27]. In two studies, dizziness was significantly more frequent in patients taking CBZ compared to patients randomised to treatment with VPA [28, 30].

In the only double-blind, placebo controlled study performed with a traditional drug [32], VPA caused dizziness, diplopia and ataxia more frequently than placebo [25]. However, statistical comparisons were not performed. In addition, since VPA was added to CBZ or PHT, in some cases these adverse effects might be caused by pharmacokinetic interactions.

In conclusion, as far as traditional AEDs are considered, PB and VPA seem to have a lower toxic potential on vestibulocerebellar and brain stem structures than PHT and CBZ.

Clinical characteristics and predisposing factors

Although both PHT and CBZ may produce cerebellar and brainstem dysfunction, there are relevant clinical differences concerning the presentation of these adverse effects. While high-dose PHT treatment causes a stable condition characterised by nystagmus and ataxia, CBZ usually determines intermittent diplopia and ataxia [33]. These intermittent side effects correlate with total and free CBZ serum levels [19]. The amplitude of the fluctuations of CBZ concentration probably influences the susceptibility to these adverse effects [19, 34]. Therefore, a controlled-release CBZ formulation is better tolerated in patients showing short CBZ half-life and wide blood level fluctuations with the traditional pharmaceutical formulation [35]. Likewise, during CBZ titration, a high rate of dosage increase favours the appearance of transient adverse effects [36]. In patients taking CBZ for trigeminal neuralgia, quantitative posturographic evaluation showed that progressive worsening of postural stability observed during titration subsided a few days after dose stabilization [37]. Moreover, compliance to high CBZ-levels seems to be higher if blood levels are increased very slowly. These data suggest adaptation to these common adverse effects, which may also appear at subtherapeutic levels [34]. However, some subjects present these adverse effects at lower dosages or do not adapt. In a population of patients whose seizures were not controlled, gaze-evoked nystagmus, dizziness, and ataxia observed during CBZ dose increases occurred at significantly lower serum concentrations, in the presence of moderate or severe cerebellar atrophy [21]. This suggests that pre-existing CNS damage may be a predisposing factor to adverse effects. It is likely that PHT-induced ataxia is not intermittent because the long drug half-life at high blood levels assures stable PHT concentrations [18, 38, 39]. This adverse effect may appear insidiously and worsen progressively even over months [17]. Sometimes ataxia may persist after drug withdrawal [38, 41-44], although it is usually reversible and dose-related [40]. Dam [45] reported Purkinje cell degeneration and astrocytic changes in patients receiving long-term PHT therapy. The role played by this drug has been debated for a long time, even though irreversible ataxia after PHT intoxication was firstly described almost 30 years ago. In fact, seizures may cause loss of Purkinje cells and cerebellar atrophy too. Seizure-induced glutamic acid activation of AMPA/quisqualate receptors may increase calcium entry into neurons and subsequent neuronal death [46]. In addition, toxic PHT levels were usually found in patients with severe epilepsy [18]. However, two main findings suggest that toxic PHT doses may cause cerebellar atrophy. PHT-induced cerebellar degeneration was also reported in nonepileptic patients [47, 48], and in some patients, neuroradiological investigations performed pre- and post- PHT intoxication showed that cerebellar atrophy appeared after the episode of drug intoxication [49, 50]. The mechanism of this peculiar PHT-induced toxic effect is still debated. Owing to its dose-dependent kinetics, PHT can slowly accumulate in the brain, reaching very high concentrations that persist for a long time after drug withdrawal [51]. In addition, PHT-induced chronic ataxia and cerebellar atrophy may predispose patients to CBZ neurotoxicity, which may persist years after the episode of intoxication [52].

New drugs

Comparisons between new and old AEDs

In several double-blind or open studies, patients with newly diagnosed epilepsy were randomised to monotherapy with a new or a traditional AED [53-64]. In none of these studies were dizziness, ataxia and diplopia significantly less frequent in patients taking the new drug, although favourable trends were observed in some of them. A metaanalysis on tolerability data, showed that the frequency of LTG-induced ataxia was significantly lower than that observed with CBZ or PHT. Also, the percentage of patients complaining of dizziness was significantly lower in patients taking the new drug, although favourable trends were observed in some of them. A positive, but not significant trend emerges also from studies in which OXC was compared to PHT [57, 58], but not from studies in which this drug was compared to VPA [59] or CBZ [60]. Studies in which GVG was compared to CBZ showed either no difference [61] or a favourable trend for GVG, in the subset of patients with dizziness [62].

GBP at the dose of 900-1800 mg/day, induced dizziness in a percentage of patients comparable that for CBZ at the dose of 600 mg/day [63]. In the most recent study, 100 and 200 mg/day of TPM were compared to 600 mg/day of CBZ or 1250 mg/day of VPA. Albeit dizziness was among the most commonly reported adverse event, no significant differences were observed [64].
In conclusion, there is evidence that LTG is better tolerated than PHT and CBZ, with respect to vestibulocerebellar and brain stem function impairment.

Comparisons between new AEDs

In the attempt to compare efficacy and tolerability of new AEDs, many metanalytical evaluations have been performed on double-blind, placebo-controlled, and add-on clinical studies [66, 67, 14, 68, 69, 70]. Odds ratios for ataxia, dizziness, fatigue, nausea, somnolence and the five more frequent adverse effects were calculated by Marson et al. [66] for LTG, GBP, GVG, TPM, TGB and by Chasewikul et al. [69] for LEV. Castillo et al. [70] reported the adverse effects that were significantly associated with OXC.

In figure 1, odds ratios (99 CI%) concerning ataxia, dizziness, diplopia (when considered), and somnolence are reported for all new drugs. For each AED, a high odds ratio value indicates a significant association with a given sign or symptom.

In a significant number of cases, active treatment with LTG and OXC was associated with ataxia, dizziness, and diplopia [66, 70]; GBP, TGB, TPM, and LEV treatment with dizziness, but not with ataxia. Finally, neither ataxia nor

![Figure 1. New antiepileptic drugs: odds ratios (99% CIs) for the adverse effects, ataxia, dizziness, diplopia and somnolence (dotted line) observed in add-on, double-blind, comparative studies. For each AED, a high odds ratio value indicates a significant association with a given sign or symptom. Data were obtained from metanalyses performed by Marson et al. (1997) for GBP, LTG, TGB, TPM, and GVG; by Castillo et al. (2001) for OXC, and Chasewikul et al. (2001) for LEV.](image-url)
dizziness were associated with GVG. Therefore, LTG and OXC seem to cause vestibulocerebellar and brain stem impairment more often than other new AEDs. Furthermore, the metanalysis showed that some of the new drugs (i.e., LTG) more selectively induce vestibulocerebellar adverse effects and are not sedative, whereas other drugs (GBP, TPM, and OXC) showed a significant association with somnolence.

However, direct comparisons between any specific adverse effect should be undertaken with caution for drugs which were assessed at different dosages: drugs that caused more adverse effects were assessed at higher dosages, which also produced more impressive response rates.

The analysis of these data also shows some discrepancies. For example, LTG and OXC seem to be very well tolerated in monotherapy, while double-blind studies indicate that these drugs may cause adverse motor effects when added to other AEDs. Pharmacokinetic [71] and/or pharmacodynamic interactions [72] could explain such results.

**Quantitative evaluation of posture control**

Computerized posturography provides a valuable tool with which to investigate vestibulocerebellar functions [73]. This technique allows us to assess quantitatively the effects on balance of neuroactive drugs [74] including AEDs [37, 75]. Data from Delker et al. [37] have been already reported. Studies performed before and after acute administration of a given drug in healthy volunteers indicate that GBP has more effects on posture control than other tested AEDs (CBZ, VPA, GVG, LTG, and the experimental drug losigamone) [75, 76].

**Neuroocular adverse effects**

The neural machinery that ultimately controls the different types of ocular motor movements is located in the brain stem and cerebellum. These anatomical pathways are very sensitive to the effect of various neuroactive drugs including AEDs [77]. PHT and CBZ may also affect ocular movements at nontoxic dosages. For example, gaze-evoked nystagmus often precedes overt toxic signs [19, 20, 21, 33]. The effects of these drugs on ocular motor structures may produce diplopia and oscillopsia.

Diplopia may be caused by lesions in various parts of the brainstem which disrupt the ocular alignment and determine inappropriate eye positioning. Oscillopsia (illusory movement of the stationary world) may be caused by lesions or dysfunction of different sites in the oculomotor system [77], resulting in an excessive motion of images upon the retina when the head is stationary (nystagmus) or during motion (inadequate vestibular ocular reflex, VOR).

Hence, several questions arise: what is the mechanism for PHT- or CBZ-induced diplopia and oscillopsia? Which structures are involved? Is the mechanism the same for all subjects? Remler et al. described eight patients with recurrent visual impairment during chronic AED treatment [78]. Transient diplopia and oscillopsia occurred in seven and six pa-

### Table 1. Ophthalmologic effects of AEDs (usually observed in patients with AEDs-induced toxic symptoms)

<table>
<thead>
<tr>
<th>AED</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Gaze-evoked nystagmus</td>
<td>Riker et al., 1978 [79]</td>
</tr>
<tr>
<td></td>
<td>Downbeat nystagmus</td>
<td>Berger and Kovacs, 1982 [80]</td>
</tr>
<tr>
<td></td>
<td>Periodic alternating nystagmus</td>
<td>Campbell, 1980 [81]</td>
</tr>
<tr>
<td></td>
<td>Partial or total gaze palsy</td>
<td>Spector et al., 1976 [82]</td>
</tr>
<tr>
<td></td>
<td>Convergence spasm</td>
<td>Guilof et al. 1980 [83]</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Gaze-evoked nystagmus</td>
<td>Umeda and Sakata, 1977 [84]</td>
</tr>
<tr>
<td></td>
<td>Downbeat nystagmus</td>
<td>Wheeler et al., 1982 [85]</td>
</tr>
<tr>
<td></td>
<td>Oculogyric crisis</td>
<td>Berchou, 1979 [86]</td>
</tr>
<tr>
<td></td>
<td>Partial or total gaze palsy</td>
<td>Mullally 1982 [87]</td>
</tr>
<tr>
<td>Phenobarbital and other barbiturates</td>
<td>Internuclear ophthalmoplegia</td>
<td>Barret et al., 1983 [88]</td>
</tr>
<tr>
<td></td>
<td>Perverted caloric responses</td>
<td>Simon, 1978 [89]</td>
</tr>
<tr>
<td></td>
<td>Vertical nystagmus</td>
<td>Lessell et al., 1975 [90]</td>
</tr>
<tr>
<td></td>
<td>Partial or total gaze palsy</td>
<td>Edis and Mastaglia, 1977 [91]</td>
</tr>
<tr>
<td></td>
<td>Impaired vergence</td>
<td>Barretet et al., 1983 [88]</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Rotary nystagmus</td>
<td>O’Donnell and Bateman, 2000 [93]</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Downbeat nystagmus</td>
<td>Hwang et al., 1995 [94]</td>
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tients, respectively. The main finding of this study was that each patient presented a different combination of disturbances (e.g. right internuclear ophthalmoplegia, right superior oblique muscle underfunction, spontaneous downbeat nystagmus, asymmetry of vertical VOR). Interestingly, the same symptoms and signs recurred in different toxic paroxysms in each patient. These results suggest interindividual differences in the susceptibility of the various oculomotor subsystems to drug effects. Accordingly, in different individuals, the same adverse effect (diplopia or oscillopsia) may be produced by different mechanisms. The great variability of AED effects on ocular movements is also evident at toxic drug levels (see table 1).

Ocular movements can be easily measured through quantitative techniques [95, 96, 97, 98]. This allows us to detect and quantify even subclinical changes. Modifications induced by different drugs have been compared during chronic therapy or after acute administration of equieffective AED doses [75, 99, 100-102].

Saccades and smooth-pursuit are the most studied ocular movements in laboratory settings. Several quantitative parameters can be measured for each kind of eye movement. For example saccades, which are the most rapid movement a subject can perform, are characterised by their precision (an excessive or reduced saccade amplitude is called saccade dysmetria and may indicate cerebellar dysfunction), peak velocity and latency. All these parameters can be evaluated quantitatively.

Smooth-pursuit analysis is usually performed through the calculation of mean eye velocity and/or gain (ratio between target velocity and eye velocity during smooth-pursuit) [77, 101]. Overt alterations of these parameters can be observed with toxic doses of AEDs [103]. Studies performed in chronically treated patients with epilepsy [95, 104] and in healthy volunteers (table 2) demonstrate that traditional AEDs and some new AEDs (e.g. GBP) affect brainstem and cerebellar structures involved in the generation of these movements.

However, the analysis of subclinical alterations often does not explain the symptoms reported by patients with toxic AED dosages. In fact, reduction of smooth-pursuit gain may seldom produce symptoms as catch-up saccades can still bring the image of the moving target onto the fovea. In

Table 2. Double-blind, placebo-controlled, cross-over, quantitative studies of ocular movements performed in healthy volunteers.

If not differently specified, all data are obtained after a single acute dose of the experimental drug and comparisons are performed versus placebo. In these studies, quantitative neuroocular examinations were performed before and subsequently for a period of six to 12 hours after intake of the experimental drug.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg)</th>
<th>Saccade</th>
<th>Smooth-pursuit</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHT 12 subjects</td>
<td>500</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>Cohen et al., 1985 [99]</td>
</tr>
<tr>
<td></td>
<td>500x 2*</td>
<td>Unchanged</td>
<td>Reduced velocity</td>
<td>Noachtar et al., 1998 [75]</td>
</tr>
<tr>
<td>CBZ 12 subjects</td>
<td>400</td>
<td>Reduction of peak velocity</td>
<td>Mild reduction of velocity</td>
<td>Tedeschi et al., 1989 [100]</td>
</tr>
<tr>
<td>CBZ 6 subjects</td>
<td>400</td>
<td>Reduction of peak velocity</td>
<td>Not performed</td>
<td>Zaccara et al., 1992 [101]</td>
</tr>
<tr>
<td></td>
<td>600</td>
<td>Reduction of peak velocity</td>
<td>Significantly worse than after OXC</td>
<td></td>
</tr>
<tr>
<td>CBZ CR 6 subjects</td>
<td>400</td>
<td>Reduction of peak velocity</td>
<td>Reduction of velocity</td>
<td>Zaccara et al., 1992 [101]</td>
</tr>
<tr>
<td>LTG 12 subjects</td>
<td>150</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>Hamilton et al., 1993 [102]</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>Unchanged</td>
<td>Reduced velocity</td>
<td></td>
</tr>
<tr>
<td>LTG 12 subjects</td>
<td>120</td>
<td>Unchanged</td>
<td>Reduction of velocity</td>
<td>Cohen et al., 1985 [99]</td>
</tr>
<tr>
<td></td>
<td>240</td>
<td>Unchanged</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OXC six subjects</td>
<td>600</td>
<td>Reduction of peak velocity**</td>
<td>Unchanged</td>
<td>Zaccara et al., 1992 [101]</td>
</tr>
</tbody>
</table>

* PHT was administered in two 500 mg doses with a time interval of 12 hours; ** Compared to baseline.
addition, a moderate alteration of saccade amplitude or peak velocity doesn’t cause any clinical symptoms [77].

**Dyskinesias**

AEDs have been associated with virtually all iatrogenically-induced extrapyramidal disorders such as dyskinesias (akathisia, chorea, athetosis, dystonia, orofacial dyskinesias, oculogyric crisis), parkinsonism, and tics. Interestingly, CBZ, VPA and GVG have been proposed in the treatment of chorea [105-109] and tardive dyskinesia [110, 111]. It has also been stated that VPA treatment may improve rigidity in some patients with end-stage parkinsonism [112].

Since almost all data concerning extrapyramidal disorders associated with AED treatment come from case reports, it may be difficult to assess the causal relationship between AED and motor disorders. Since the first description by Peters [113], at least 130 cases of anticonvulsant-induced dyskinesia have been described. More than two thirds of them have been associated with PHT (table 3).

**Traditional drugs**

**PHT-induced dyskinesia**

In 1993, Harrison et al. reviewed 77 cases of PHT-induced dyskinesia from the literature and described two new cases [114]. Since then at least 12 further cases have been reported [115-121]. Frequently, patients had more than one type of dyskinesia. Choreoathetosis was observed in 91% of cases [114]. Orofacial dyskinesia and dystonia were less frequent and were sporadically observed in the absence of choreoathetosis [114]. Ballism has been rarely reported and was the sole manifestation in only one patient [122].

**Table 3. Number of patients described in various case reports, with dyskinesia (chorea, athetosis, dystonia, oral dyskinesia, akatisia), parkinsonism or tics associated with AEDs.**

<table>
<thead>
<tr>
<th>AED</th>
<th>Dyskinesias</th>
<th>Parkinsonism</th>
<th>Tics</th>
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<tbody>
<tr>
<td>Phenytoin</td>
<td>91 [114-121]</td>
<td>2 [152, 165]</td>
<td>1 [167]</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>6 [131-135]</td>
<td>13 [166, 168-171, 173]</td>
<td></td>
</tr>
<tr>
<td>Phenoarbital</td>
<td>4 [138-141]</td>
<td>3 [166]</td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>4 [136, 137]</td>
<td>19 [155-164]</td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>4 [142, 143]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Felbamate</td>
<td>2 [148]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>8 [144-147]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>3 [130]</td>
<td>8 [174, 175]</td>
<td></td>
</tr>
<tr>
<td>Tiagabine</td>
<td>3 [149]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vigabatrın</td>
<td>4 [150, 151]</td>
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* Reference numbers in parenthesis.

These complications may be observed at introduction of the drug [116, 123] or after a dosage increase [114]. In some patients, dyskinesia was observed at toxic PHT levels and often subsided after drug level normalization [123]. Transient hyperkinesia was also observed after a single intravenous PHT perfusion at non-toxic drug blood levels [124].

Harrison et al. [114] reported that in more than 50% of patients, PHT levels were in the toxic range (greater than 21 mg/L). Drug concentrations were less than 10 mg/L in 7% of patients and in the standard range in about 25%. Furthermore, 68% of patients with this complication were on polytherapy. Pharmacokinetic interactions could explain the increased risk of PHT-induced dyskinesia in patients on polytherapy.

Choreiform movements have been described in two patients treated with PHT and VPA. In these cases, chorea developed 30 minutes to three hours after VPA intake, and the duration of the episodes varied between 30 minutes and eight hours. In both patients, replacement of VPA with divalproex sodium resulted in resolution of chorea [125]. Since VPA concentration peaks displace PHT from its binding sites [126], we can speculate that this would increase PHT free fractions and cause toxic symptoms.

A high free fraction of PHT plasma concentration was also reported in a patient with PHT-induced choreoathetosis [127]. Pharmacodynamic interactions affecting central dopaminergic pathways may also play a role in some cases. In an animal model, methamphetamine-induced stereotyped behaviour was potentiated by pretreatment with PHT [128]. A pharmacodynamic interaction between AEDs and amphetamine-like stimulants, sometimes prescribed to counteract AED-induced somnolence, can increase the risk of this adverse effect [129].

Furthermore, chorea has been recently described in three patients taking PHT and LTG [130]. Since each drug, when administered alone, did not cause such an adverse effect, an additive or synergistic effect was postulated. On the other hand, since CBZ and VPA can be useful in chorea treatment [105-109], we could also speculate that coadministration of these drugs with PHT might have a protective effect in some patients.

Another relevant issue is patient predisposition. Basal ganglia damage [116] and mental retardation [114] have been frequently reported in patients with PHT-induced chorea. Also some epileptic syndromes seem to be associated with a higher risk for these adverse effects. Patients with severe myoclonic epilepsy have been considered particularly vulnerable to PHT-induced choreoathetosis [120].

In conclusion, evidence that PHT treatment may cause dyskinesias is provided by the large number of patients in which dyskinesia has been associated with PHT (table 3), the temporal relationship between disturbances and drug
administration and withdrawal, and the reoccurrence of the adverse effects when the drug was rechallenged [123].

Other traditional AEDs

As far as all other AEDs are concerned, only a few cases have been described, often without a clear temporal relationship between drug administration and the appearance of dyskinesias (table 3).

During CBZ treatment, dyskinesias have been observed only with toxic levels [131-134]. Several clinical studies indicate a possible CBZ efficacy in patients with non-hereditary chorea [106], namely rheumatic chorea [108, 109]. A pharmacodynamic interaction has been suggested to explain tardive dyskinesia observed in a patient taking lithium and CBZ [135].

In only two case reports was VPA treatment associated with dyskinesias [136, 137]. However, in one of these patients, choreiform movements ceased only two months after VPA withdrawal [137]. In addition, two out of three cases described by Lancman and Asconape [136] also received PHT. Finally, VPA also has a possible therapeutic role in age-related [107] and Sydenham’s chorea [105] and in tardive dyskinesia [111].

Phenobarbital [138-141] and ethosuximide [142, 143] have also been exceptionally associated with diskinesia.

New AEDs

Some recent publications indicate that dyskinesias have been rarely observed during treatment with new AEDs. Choreoathetosis was reported in eight epileptic patients taking GBP. In all patients, symptoms ceased with drug discontinuation and in two cases, recurrence of choreiform movements was observed when the drug was reintroduced [144-147].

For all other new AEDs the evidence is weaker. Two children taking FBM developed involuntary movements. In both cases, disturbances resolved after drug discontinuation but no rechallenge was attempted [148].

Three patients receiving a combination of LTG and PHT developed chorea [130]. In all cases, chorea improved with tapering of one of the medications. The authors hypothesized a pharmacodynamic interaction. However, LTG alone never induced abnormal movements.

Wolanczyk and Grabowska-Gryzyb [149] described transient dystonia in three patients treated with TGB. However, in all cases, involuntary movements resolved spontaneously without TGB discontinuation or dose reduction. Akathisia or perioral dyskinesia were observed in four patients treated with GVG [150, 151] but a therapeutic effect of this drug was reported in patients with tardive dyskinesia and other movement disorders [110].

Pathophysiology

The role of basal ganglia in motor control is complex and involves multiple neurotransmitters and neuronal networks. AEDs have different and sometimes multiple mechanisms of action. Therefore, we can speculate that different AEDs might affect basal ganglia through different mechanisms. However, the final effect should be dysfunction of dopaminergic systems at the basal ganglia level.

It is known that toxic PHT doses decrease in vitro neuronal calcium influx and inhibit dopamine re-uptake and breakdown [114]. On the other hand, similarities between PHT-induced dyskinesias and neuroleptic-induced extrapyramidal symptoms lead to the consideration of PHT-induced dyskinesia as a manifestation of dopamine blockade or depletion in the basal ganglia, resulting in supersensitivity of dopamine receptors [152]. This hypothesis was rejected since it has been recently demonstrated that PHT does not alter dopamine D2 receptor density or affinity in animal models [153]. As regards other AEDs, it has been speculated that the potentiation of GABAergic effects and/or inhibition of the excitatory neurotransmission might indirectly cause dyskinesias. GABA increase may enhance striatal dopamine levels by attenuation of dopamine turnover [140]. Moreover, inhibition of glutamatergic transmission could potentiate the dopaminergic basal ganglia pathways [154] since glutamate is the principal excitatory neurotransmitter in the cortico-striatal pathways suppressing dopamine release in the striatum. These hypothetical mechanisms have been suggested to explain dyskinesias during treatment with the GABAergic drugs GVG, TGB and VPA and with LTG (which inhibits glutamatergic pathways).

Parkinsonism

Although VPA can reduce rigidity in end-stage parkinsonism [112], many recent reports suggest that this drug may cause a reversible parkinsonian syndrome [155-163]. This disturbance may appear within few days of VPA treatment [156] or may have an insidious onset and become clearly detectable after many years [157, 159, 161]. In some cases, reversible dementia and brain pseudoatrophy were associated with parkinsonism [161]. After VPA discontinuation, such symptoms gradually disappeared within weeks or months [158, 159, 161].

Armon et al. [164] followed, for at least one year, 32 epileptic patients taking VPA and found various degrees of parkinsonism and cognitive impairment, which always improved after drug withdrawal. It is possible that the frequency of VPA-induced parkinsonism is underestimated due to its insidious onset. Also PHT treatment is sometimes associated with parkinsonism [152, 165].

Tics

Tics are infrequently observed during AED treatment (table 3). CBZ and LTG are more often implicated although
exceptional cases were also reported with PB [166] or PHT [167]. Therapeutic CBZ levels may be associated with the appearance of tics in normal children [166, 168-172] or exacerbation of tics in patients with movement disorders [173]. Chronic LTG treatment at therapeutic dosages can also induce tics [174, 175]. One out of three children described by Lombroso [174] and two out of five described by Sotero et al. [175] had recurrence of their tics after reintroduction of LTG. Patients with severe language dysfunction and acquired epileptic aphasia (Landau Kleffner syndrome) seem to be more susceptible to this uncommon side effect [166, 175].

Although their pathogenesis is still debated, tics are thought to be caused by a dysfunction of dopaminergic circuits at the basal ganglia level, consisting of an increase in dopaminergic activity [176]. In fact, tics are induced by dopaminergic drugs and inhibited by dopamine receptor antagonists, such as haloperidol.

CBZ has been shown to increase dopamine, its metabolites, and its precursors in the striatum and hippocampus at therapeutic plasma concentrations [177]. LTG does not seem to have any significant activity on dopamine receptors [178]. The possible pathophysiological mechanism of tics observed with this drug [175] consists of an inhibition of glutamatergic pathways, which may potentiate dopaminergic transmission (see above).

Myoclonus

The term myoclonus indicates an involuntary, jerky muscle contraction (positive myoclonus), or a brief lapse of muscle activity (negative myoclonus). Myoclonus can be epileptic (when time-locked with EEG epileptiform discharges, [179]), or non-epileptic [180]. All these types of myoclonus may be induced by various AEDs. Positive or negative epileptic myoclonus can reflect AED-induced worsening of epilepsy, i.e. increased seizure frequency or appearance of a new type of seizure; for a detailed review of this phenomenon see [181].

Traditional drugs

PHT may directly worsen myoclonic jerks in several epilepsy syndromes [182]. In patients with neurotoxic symptoms, non-epileptic myoclonus was also sporadically reported [182-185]. CBZ is the AED most frequently implicated in seizure worsening [181]. In juvenile myoclonic epilepsy, the frequency of myoclonic jerks can be increased by CBZ [186]. Furthermore, CBZ has been associated with the appearance of myoclonus in benign rolandic epilepsy. Also epileptic negative myoclonus has been described in these cases [187, 188]. Non-epileptic myoclonus has been reported in patients with various epileptic disorders [152, 189, 180, 190, 191]. However, in some cases, the epileptic origin could not be definitely ruled out due to the lack of EEG data [152].

The appearance of myoclonus at the beginning or during VPA treatment may indicate toxic encephalopathy [194, 195] with alteration of consciousness and hyperammonemia, not necessarily associated with high serum drug levels. In six patients with epilepsy who developed a valproate-related hyperammonemic stupor, a neurophysiological evaluation suggested a nonepileptic origin of the negative myoclonus [193]. The appearance of myoclonic seizures [192] after VPA intoxication has been reported just in one case.

In conclusion, some traditional AEDs such as PHT or CBZ may induce both epileptic and non-epileptic myoclonus, while VPA-induced toxic encephalopathy can be associated with non-epileptic myoclonus.

New drugs

GVG can precipitate myoclonic jerks and induce myoclonic status in susceptible patients. These abnormalities are correlated with paroxysmal EEG discharges [179, 196]. Newly diagnosed adult patients with partial and primarily or secondarily generalised tonic-clonic seizures were randomised to GVG or CBZ monotherapy. Myoclonic jerk frequency was 14% in the GVG group and 2% in the CBZ group [62]. In 16 out of 20 children affected by severe myoclonic epilepsy, a seizure worsening was observed when LTG was added to the treatment [197]. Myoclonic seizures increased more frequently than other seizure types. Continuous and disabling myoclonic jerks also appeared in two adult patients treated with high doses of LTG [198]. Finally, myoclonic status was observed in a child with Lennox-Gastaut syndrome when the LTG dose was increased to 20 mg/kg [199].

GBP treatment is frequently associated with the appearance of myoclonus. In a patient with Lennox-Gastaut syndrome, the administration of this drug induced a dramatic exacerbation of atypical absence and myoclonic seizures [200]. However, in two patients with partial epilepsy, myoclonic jerks observed during GBP treatment showed no EEG correlation, suggesting a non-epileptic origin [145].

Recently, Asconape et al. [201] reviewed 104 consecutive patients treated with GBP. Myoclonus was found in 13 patients (12.5%). Most patients had new-onset myoclonus, whereas two cases showed exacerbation of a preexisting disorder. In three patients the neurophysiological evaluation showed that myoclonus was non-epileptic. This population was characterised by a relatively large proportion of patients with mental retardation and/or diffuse brain damage. These patients are probably at higher risk for the development of myoclonus and other movement disorders. However, the authors stated that myoclonus
Tremor

Tremor is defined as an involuntary, rhythmic, oscillatory movement of a body part [203] and may be induced by many drugs [204]. Since 1979, it has been known that VPA may cause tremor [205]. This is usually characterised by a high frequency and low-amplitude, resembling essential or adrenergic tremor [206]. There is no close correlation with plasma levels, although tremor is usually observed at dosages greater than 750 mg/day [207]. In a double-blind study in which VPA was added to PHT or CBZ, tremor was observed in 25% of patients taking the active drug and in 6% of patients randomised to placebo [206]. In a study performed with accelerometric recordings, tremor was observed in 20 out of 25 subjects treated with VPA [207]. Propranolol, amantadine [208], and acetazolamide [209] may be used to treat this disturbance when particularly disabling. Finally, the association of LTG with VPA seems to worsen this adverse effect [210].

Also, some new AEDs have been associated with tremors. In the meta-analysis performed by Marson et al. [66] on key double-blind studies, tremor turned out to be one of the five most frequent adverse effects induced by TGB, and was significantly associated with the active treatment. An analysis of adverse effects observed in all clinical studies performed with this drug showed that tremor is more frequently observed at high doses (> 36 mg/day), and is correlated with drug concentration [211]. Interestingly, many traditional AEDs have been successfully used in the treatment of tremor. It is known that PB and PRI are effective in the treatment of essential tremor [212] and that CBZ has shown efficacy in the treatment of cerebellar tremors [213]. Of the new AEDs, the efficacy of GBP [214, 215] and TPM [216, 217] has been documented by small, double-blind studies and open observations. Also, FBM has been used in a few patients with essential tremor [217] although its high toxicity prevents any future use in this condition. Consequently, controlled studies have not been performed.

General conclusions

Many adverse CNS effects are predictable, dose-dependent and resolve with dose reduction. Therefore, they can be classified as type A [1]. However, some rare adverse effects such as dyskinesias or tics are more difficult to classify. In fact, even if characterized by a dose-response relationship, their appearance is unpredictable and host-dependent (type B).

We think that more attention should be paid to the understanding of the mechanisms that cause the various adverse effects. From a theoretical point of view, the same adverse effect can be induced by different mechanisms. For instance, diplopia or oscillopsia can be caused by the action of a drug on different brainstem structures [78]. This means that even a simple and frequent adverse effect may be somehow idiosyncratic since in single subjects it is caused by a drug effect on a selectively sensitive, CNS structure.

Several years ago, we studied ballistic arm movements in nine patients with PHT intoxication [219]. During the overdose period, such patients displayed a wide variability in the type and severity of the abnormalities of ballistic motor performance with no relationship to PHT plasma levels. Different abnormalities were interpreted as the effects of PHT on distinct cerebellar structures and, in one case, on extrapyramidal ganglia. Also in this case, similar clinical symptoms (dysmetria) of PHT overdose were caused by different mechanisms.

Hence, for a better characterization of the pathophysiology of such adverse effects, patients with toxic symptoms should be carefully evaluated during the toxic episode. Studies performed in healthy volunteers, although useful, cannot clarify the mechanisms of toxic effects in the single patient.

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References


