Antiepileptic drugs and their impact on balance

Terry D Fife[1] & Joseph Sirven[2]
†Author for correspondence

[1]University of Arizona College of Medicine, Barrow Neurological Institute Visiting Scientist, Mayo Clinic Scottsdale Phoenix, Arizona, USA
Tel.: +1 480 614 2200; Fax: +1 480 614 2205; E-mail: tfife@email.arizona.edu
[2]Mayo Clinic, Mayo Comprehensive Epilepsy Program, Mayo Clinic College of Medicine, Scottsdale Phoenix, Arizona, USA
Tel.: +1 480 342 2581; E-mail: sirven.joseph@mayo.edu

Antiepileptic drugs (AEDs) are being used with increasing frequency, not only to manage epilepsy, but also in the treatment of other conditions including neuropathic pain, migraine headaches and psychiatric conditions requiring mood stabilization. Although AEDs as a class are commonly prescribed in older patients and those with a predisposition to imbalance, the effect these drugs exert on gait and equilibrium has received very little study. Data from controlled efficacy and safety trials suggests that some AEDs are more apt to affect balance than others, even at therapeutic doses. In particular, phenytoin, primidone and phenobarbital produce more dizziness than some of the newer AEDs such as lamotrigine, levetiracetam and oxcarbazepine. For some of the other new AEDs, the data are simply not sufficient to estimate their effect on balance. This article reviews the current evidence that may guide the clinician in choosing a medication likely to have a low impact on gait and balance. Considering the risks and morbidity associated with imbalance and falls, particularly in the elderly, the direct effects of AEDs on balance should be examined further.

Keywords: adverse events, anticonvulsant medications, antiepileptic drugs, ataxia, dizziness, equilibrium, imbalance

future medicine

Antiepileptic drug use is common

Approximately 1.5% of older Americans have a seizure disorder [1] requiring an antiepileptic medication (AED). In individuals 65 years or older in long-term care facilities, more than 10% take at least one AED [2]. In a study of 21,551 nursing home residents, 12% received AEDs. Phenytoin alone accounted for 52% of these cases, carbamazepine, phenobarbital or valproic acid accounted for 38%, and 10% were receiving other AEDs [3]. Nursing home residents also take other medications that may result in adverse drug interactions, which may be severe [4].

AEDs are also used for conditions other than epilepsy. Garrard and colleagues found that of the 7.7% of nursing home residents using AEDs, 42% were taking them for reasons other than epilepsy [5]. Furthermore, of the 3% that started to take AEDs after admission, more than three-quarters received an AED for a non-seizure related indication. AEDs are commonly being used to treat post herpetic neuralgia, migraine and headaches, diabetic neuropathy, neuropathic pain, bipolar affective disorder, trigeminal neuralgia and other conditions [6].

Before 1990, there were six major AEDs for the treatment of epilepsy. In the past 15 years gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam and zonisamide have been approved for use in epilepsy and an additional agent, pregabalin, is expected to be available for use this year. As more and more older patients are prescribed AEDs for epilepsy or other indications, clinicians are increasingly faced with the need to understand the special considerations in older people and the potential negative impact that side effects of these medications have on quality of life [7].

Dizziness & ataxia are common AED side effects

Dizziness and ataxia are among the most commonly listed side effects of AEDs. Results from the Veterans Administration (VA) Cooperative study found that dose-dependent adverse events are common, and unsteadiness and dizziness are particularly frequent [8]. Young and colleagues found ataxia was present in 54% of 41 institutionalized patients with epilepsy [9]. In a retrospective chart review of subjects aged 70 years or older with idiopathic generalized epilepsy, four of five subjects identified suffered from balance disorders and falls. All of these patients had received chronic antiepileptic drug therapy [10].

Phenytoin is still the most commonly used AED in older people in nursing facilities [5]. Approximately 1% of all Medicare beneficiaries take phenytoin [3], and this number increases to 6% for those confined to nursing homes [4]. In many studies there is a high rate of adverse events, including imbalance and dizziness.

The hazards of imbalance in older people

Gait imbalance is a common problem in older individuals [11] and may be more severe in those

taking AEDs. Falls and skeletal fractures are two to six times more frequent in epileptic patients than in the general population. Less than half are attributable to seizures [12], suggesting that many fractures may result from falls associated with drug-related dizziness and ataxia [13,14], especially in the case of phenytoin [15].

Susceptibility to drug-induced ataxia & dizziness

Ataxia and dizziness are often dose-dependent adverse effects, especially with carbamazepine and phenytoin, although idiosyncratic reactions to AEDs may also produce ataxia in rare instances [16]. In addition, patients with pre-existing balance disorders may be especially susceptible to the effects of some antiepileptics. Patients with cerebellar atrophy identified by blinded magnetic resonance (MR) imaging analysis were found to be more sensitive to the effects of carbamazepine on balance [17]. Aging itself results in loss of Purkinje cells in the cerebellum [18] and decreased blood flow measurements as indicated by single photon emission computed tomography SPECT imaging [19], so older patients may be inherently more vulnerable to medications that interfere cerebellar function. Carbamazepine, even at low doses, can impair balance as determined by posturography in patients with coexisting cerebellar atrophy [17]. Patients using phenytoin for epilepsy are more likely to exhibit cerebellar atrophy on MR imaging than age-matched controls [20], and studies in cats and rats show Purkinje cell loss and swelling of Bergmann's glia when exposed to high doses of phenytoin for as little as 2 weeks [21]. Balance may also be impaired when two or more AEDs are used together [22]. These studies suggest that medications for epilepsy may contribute significantly to dizziness, imbalance and falling, particularly in the elderly. **Figure 1** illustrates how patients' balance, and thus their quality of life, may be reduced by AEDs.

Studies quantifying sway in patients taking AEDs

Very little is known about the specific effects of AEDs on balance and dizziness. Although these are common adverse events in controlled trials, little detail about the type and severity of these symptoms can be determined since many of the trials are intended to assess efficacy or broadly examine adverse events. Consequently, dizziness, gait unsteadiness and ataxia remain unexplored adverse events, often with different definitions between studies.

A few studies have attempted to quantitatively assess the postural and balance effects of AEDs. In one study, sway was greater in those taking more than one AED [22]. Benzodiazepines have been studied with regard to their effects on sway, and lorazepam was associated with increased sway compared with some other benzodiazepines [23]. Some AEDs may cause more imbalance, while others may produce more effects on ocular motility and dizziness. For example, carbamazepine produces more pronounced effects in normal volunteers on saccadic eye movements than gabapentin, whereas gabapentin produces a greater effect on body sway [24]. In a study of 22 patients with trigeminal neuralgia started on carbamazepine, Delcker and colleagues found alterations in posturographic measurements [25].

Balance effects of selected AEDs from clinical trials

The following is a summary of the findings of mostly randomized, controlled trials and the incidence of dizziness, gait imbalance or ataxia in patients taking these drugs versus those taking placebo.

Gabapentin

In the recent Neurontin Evaluation of Outcomes in Neurological practice (NEON) study of gabapentin as an add-on medication, dizziness occurred in 9% of patients [26]. In intractable partial epilepsy, somnolence, dizziness and fatigue were among the most frequent side effects [27]. Dizziness was more likely following rapid initiation of gabapentin at a dose of 900 mg in a single day than if the titration was gradual over 3 days [28].

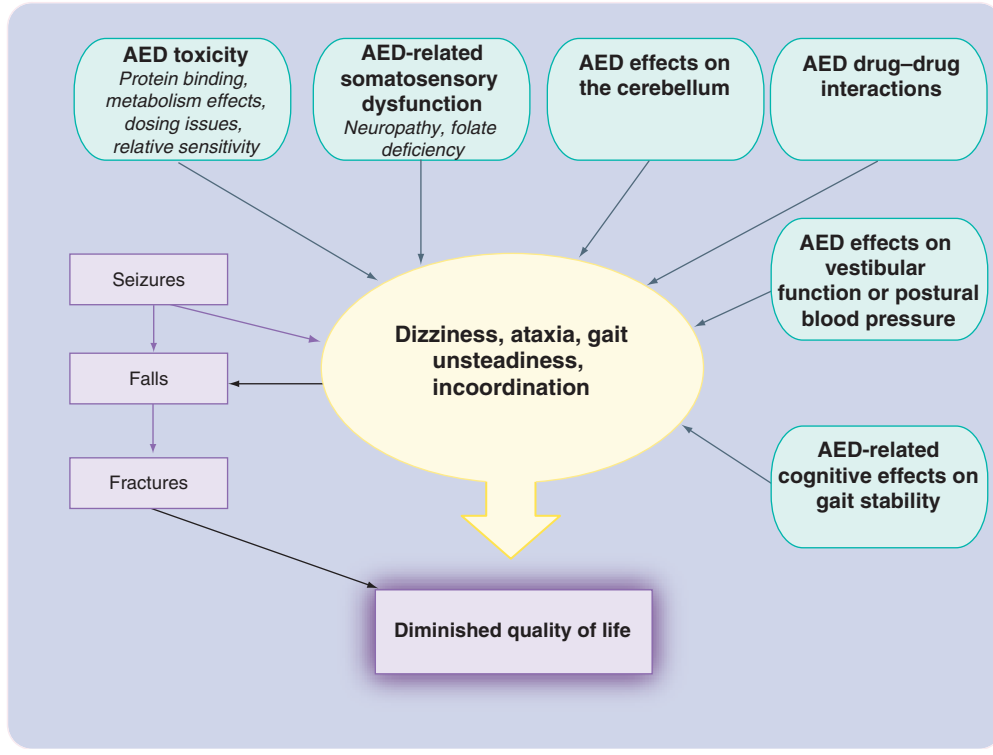
Another study found significantly more dizziness (20.2%) in gabapentin (<1800 mg/day) compared with placebo (7.4%), but found no difference between gabapentin in doses greater than 1800 mg/day compared with placebo [29]. This suggests that dizziness may be more often idiosyncratic than dose-related in patients taking gabapentin. In a meta-analysis, however, both dizziness and ataxia occurred significantly more often with gabapentin than with placebo [30].

Other studies of gabapentin in patients with postherpetic neuralgia found dizziness to be one of the most common adverse events, but of low frequency and mild in severity [31,32].

Lamotrigine

The most common side effects from double-blind controlled trials of lamotrigine in the treatment of refractory partial seizures were ataxia,

Figure 1. The complex interplay between dizziness from antiepileptic drugs (AEDs), seizures, ataxia, fractures and quality of life.



dizziness, diplopia, somnolence and headache [33–35]. A meta-analysis review found dizziness and ataxia were significantly more likely to occur in patients taking lamotrigine than in those taking placebo [30]. Nevertheless, lamotrigine appeared to be the least likely drug among the newer AEDs to cause treatment discontinuation. Another study found dizziness to be the most frequent side effect but its incidence was only 1.3% and generally deemed to be of mild severity [36].

Phenytoin

The most recent data on phenytoin was derived from comparison trials with newer AEDs. Adverse events, particularly ataxia and nystagmus, were more common with phenytoin than with phenobarbital, carbamazepine or valproate in one multicenter survey among epilepsy patients in Italy [37].

It has been recommended that phenytoin should be avoided in patients with intellectual disability or balance disturbances [38].

Topiramate

The most common adverse events in a number of controlled studies using topiramate to treat intractable partial epilepsy include somnolence, fatigue, nausea, anorexia, weight loss, paresthesias, psychomotor slowing and confusion, dizziness and headache [39–43].

In a meta-analysis it was found that dizziness was more likely to be reported in patients taking topiramate than in those taking placebo [30].

Oxcarbazepine

A long-term tolerability and efficacy trial of oxcarbazepine in 87 patients with refractory partial epilepsy found dizziness among the most common adverse events; however it appeared to be mild and often transient [44]. Similarly, other reports have concluded that dizziness and ataxia are common but relatively mild side effects associated with oxcarbazepine [45,46]. Another controlled dose-ranging study, however, did find a dose-related and substantial increase in dizziness, vertigo, ataxia and gait disturbance compared with placebo [47]

In a study of older people with epilepsy, dizziness occurred in 17%, second only to vomiting (19%) in frequency. Nevertheless, there was no difference compared with placebo in the rate of trial discontinuation due to side effects [48].

Table 1. Selected data comparing AED effects on balance and dizziness.

Drugs assessed	n	Population	Results	AED with less impact on balance	Ref.
GBP, CBZ	275	Adolescents and adults on monotherapy	In a controlled study, 24% discontinued carbamazepine compared with 13.5% for gabapentin. Dizziness was more frequent in those taking carbamazepine than in those taking gabapentin	GBP	[64]
LTG, CBZ	150	Newly diagnosed epilepsy in patients with median age 77 years randomly treated with LTG or CBZ in double-blind treatment	10% taking LTG reported dizziness, 17% of those on CBZ reported dizziness	LTG	[65]
PHT, LTG	181	Controlled trial of patients with new onset epilepsy randomized to monotherapy treatment with either PHT or LTG, ages 13–74, median age 28 years	PHT had much higher rates of asthenia (29% PHT vs 16% LTG), somnolence (28% vs 7%), and ataxia (11% vs 0)	LTG	[66]
VPA, CBZ, TPM	613	Pediatric and adult patients aged 6 years and older with partial and primary generalized epilepsy	Early termination rates of 23% for TPM and VPA groups, 25% for CBZ. No significant difference in the rate of dizziness among drugs	TPM=VPA=CBZ	[67]
CBZ, GBP, LTG	593	Mean age 73, predominantly males enrolled from the Veteran's Association Cooperative Study 428, double blind randomized longitudinal study	Dizziness and unsteady gait were dose-dependent adverse events more common in patients taking CBZ than in those on LTG or GBP	LTG=GBP	[8]
GBP, CBZ	12	Healthy volunteers in a double- blinded cross-over study of acute effects of these AEDs on eye movements and balance	CBZ caused more changes in saccades, GBP caused more body sway with eyes open or closed as measured by posturography	CBZ	[24]
GBP, CBZ, LTG	30	Healthy epileptics on monotherapy, age ≥50 years, none of the patients previously complained of dizziness or imbalance	Pooled analysis showed that those on LTG had slightly better balance than GBP or CBZ on ataxia scale but all had similar posturography responses	LTG≥GBP=CBZ	[68]
OXC, PHT	287	Adults with previously untreated partial and primary generalized epilepsy	Dizziness was only slightly more in PHT (15.5%) than with OXC (13.2%); nystagmus was more common with PTH; overall discontinuation was also higher among those patients on PHT	OXC≥PHT	[69]
OXC, VPA	249	Adults with newly diagnosed partial and primary generalized epilepsy	No significant differences in trial termination rates, or adverse events of dizziness or ataxia	OXC=VPA	[70]
OXC, CBZ	235	Adults with primary and secondarily generalized epilepsy	Discontinuation rates due to adverse events were 26% in patients on CBZ and 14% on OXC; however the side effects of dizziness and ataxia were fairly similar	OXC≥CBZ	[71]
LTG, VPA	156	Study of LTG or VPA as add-on treatment in adult patients with intractable partial epilepsy	Discontinuation rates due to adverse events were 11% for LTG and 5% for VPA. Dizziness was among the most commonly listed side effects in both groups	VPA=LTG	[72]
GBP, LTG, CBZ	593	Newly diagnosed epilepsy in those >65 years of age	At baseline, 76% of patients had an abnormality of gait or station (no specifics); 29% of patients from each group reported a new gait problem or dizziness among those completing at least one follow-up visit	GBP=LTG=CBZ	[73]

AED: Antiepileptic drug; CBZ: Carbamazepine; GBP: gabapentin; LTG: Lamotrigine; OXC: Oxcarbamepine; PHT: Phenytoin; TPM: Topriramate; VPA: Valproate.

Zonisamide

Zonisamide was significantly associated with ataxia in patients treated for partial epilepsy with a nearly fourfold likelihood (odds ratio 3.94) of complaints of ataxia in patients taking zonisamide compared with those taking placebo [49]. However, no details of the nature of ataxia were available. In a meta-analysis, ataxia and dizziness were more likely to occur in patients taking zonisamide than in those taking placebo [30].

In a controlled safety and efficacy trial of zonisamide, dizziness was among the most common symptoms but was mild and mainly occurred in the titration phase [50]. Other researchers have also found dizziness to be common but mild in patients with refractory partial epilepsy [51,52].

Levetiracetam

In a subset of 78 patients aged 65 years or older in the KEEPER™ trial, 15% discontinued the trial due to side effects including 16.7% incidence of somnolence. Dizziness or ataxia were noted in 10% of patients [53].

Dizziness was reported in 5.8% of patients, second only to somnolence (11.7%), in the Safety of Keppra as Adjunctive Therapy in Epilepsy (SKATE) trial in Spain [55]. Another study of levetiracetam use in patients aged 65 years or older with anxiety and cognitive disorders, found dizziness to be among the most common adverse events leading to study discontinuation; however, the incidence was very low and the authors concluded levetiracetam to be suitable in older people due to its tolerability [55]. In all studies reviewed in this article, levetiracetam had a relatively low incidence of dizziness or gait imbalance.

Tiagabine

In a review of Cochrane Epilepsy Group trials, dizziness was found to be significantly associated with tiagabine add-on treatment for refractory partial epilepsy [56].

Another study using tiagabine as an add-on treatment of partial epilepsy revealed dizziness and incoordination as the most frequent symptoms in the 22% reporting an adverse event [57].

Dizziness and tremor were side effects more likely to be associated with tiagabine than with placebo in a meta-analysis [30].

Primidone

Primidone is significantly associated with dizziness. In a comparison study with carbamazepine, phenobarbital and phenytoin, primidone was notably associated with side effects, the most common among them was dizziness [58].

Phenobarbital

Truncal ataxia was present in 28 of 95 outpatients receiving chronic treatment with phenobarbital for seizures [59]. Those with ataxia had lower folate levels than their non-ataxic counterparts, raising questions regarding the role of folate in ataxia in some of these patients.

AED drug overdose reports

Overdoses of AEDs may provide some insight into the effects these drugs have at therapeutic dosages. In a retrospective review of patients following gabapentin overdose, the authors reported no symptoms or minimal toxicity in most and dizziness in only 2 of 20 patients [60]. Gabapentin displays dose-dependent absorption, which may explain why overdose does not produce more adverse effects. Lamotrigine toxicity in cases reported to a poison control center most commonly produced no toxic clinical effects but among the symptoms reported, ataxia and dizziness occurred in less than 5% of 493 cases. Phenytoin, on the other hand, is well known to produced nystagmus, severe ataxia, dysarthria and dizziness that are dose related and increased the risk of falls [61,62]. In patients with carbamazepine overdose that recover, coma, somnolence and cerebellar ataxia are the most common adverse effects [63].

Which AEDs have the lowest incidence of dizziness or ataxia?

Table 1 lists comparison trials and the reported data on balance difficulty. These studies vary in patient population, thus comparisons of their adverse effects must be viewed with this in mind. There have been no systematic studies comparing one AED to another for the purpose of evaluating balance. A meta-analysis of prior AED studies did not clarify the comparative incidence of dizziness or gait disorders induced by these or any of the other AEDs [30].

Conclusions

Review of the clinical efficacy and safety trials data on balance suggests that phenytoin and primidone are probably more likely to cause dizziness or imbalance. Data from these and other studies also indicates that dizziness is among the most commonly reported adverse events for all anticonvulsants, but in some cases it is mild or transient especially for most of the newer AEDs.

Previously reported expert consensus recommendations favored the use of lamotrigine, gabapentin, oxcarbazepine and carbamazepine over phenobarbital and phenytoin as treatment for newly diagnosed elderly patients with epilepsy, since they appear to cause fewer adverse events including dizziness, unsteady gait and ataxia [74]. From review of the clinical studies, it appears that levetiracetam had the fewest adverse effects on balance. Some studies have suggested that oxcarbazepine and lamotrigine have dizziness of relatively mild severity but the data are insufficient to draw a firm conclusion. Additional studies specifically designed to assess the effects of AEDs on balance are needed before we can know with confidence which AEDs have the least negative impact on balance.

Future perspective

Given the importance of balance on independent living, quality of life, fall risk and cost of care, it is likely that more attention will be given to the gait and balance effects associated with AED use. The rapid introduction of so many anticonvulsants over the past 15 years has not permitted a full exploration of the factors important in choosing one over the other. Future studies using ataxia rating scales, balance measures, posturography and dynamic gait measurements may provide the insight needed to choose medications best suited for patients in whom balance problems are of particular concern.

Executive summary

Introduction

- There are a multitude of new antiepileptic medications now available but we lack detailed information about how each one affects the gait, balance and equilibrium of the patient.

Antiepileptic drug use is common

- Antiepileptic medications are used frequently both for epilepsy and other conditions. The widespread use of these medications underscores why it is importance to know all of their negative effects.

Dizziness and ataxia are common antiepileptic drug (AED) side effects

- Dizziness, gait unsteadiness and ataxia are among the most common adverse events reported in clinical trials of antiepileptic medications and may occur even at therapeutic dosages.

The hazards of imbalance in older people

- Imbalance and dizziness are linked to reduced quality of life and increased risk of fall. Despite the frequency of balance effects from antiepileptic medications, there is very little data to guide the choice of drug in older people or those with pre-existing balance problems.

Susceptibility to drug-induced ataxia and dizziness

- Older people may be particularly vulnerable to medications that have a negative impact on balance since they are more prone to deterioration of balance from a variety of other factors.

Studies of balance patients taking AEDs

- A few studies have used posturography to determine the effects medications can have on postural sway but there is very little data on this subject.

Balance effects of selected AEDs from clinical trials

- Inferences can be made by reviewing the data from controlled clinical efficacy and safety trials but details are sparse or absent and it is difficult to compare one medication to another using this data.

AED drug overdose reports

- Clinical symptoms in patients surviving AED overdoses indicates that levetiracetam and lamotrigine produce relatively little dizziness or ataxia even at toxic doses, which is in contrast with the known toxicities of phenytoin and carbamazepine.

Which AEDs have the lowest incidence of dizziness or ataxia?

- Taking data from adverse events in clinical trials is an imperfect method of determining the relative impact each drug has on equilibrium. However, data suggests that levetiracetam has relatively little effect on balance. Other medications such as lamotrigine, oxcarbazepine and possibly several other new generation anticonvulsants may have only a moderate effect on balance but further studies are needed to confirm this impression.
- Primidone, phenobarbital and phenytoin and, to a slightly lesser degree, carbamazepine appear to produce a greater impairment of balance.
- Considering the risks and morbidity associated with imbalance and falling in the elderly, the direct effects of AEDs on balance is a seriously understudied area. Prospective trials are needed to better understand the relative effects antiepileptic medications have on balance.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Leppik IE, Birnbaum A: Epilepsy in the elderly. *Semin. Neurology* 22, 309–320 (2002).
2. Cloyd JC, Lackner TE, Leppik IE: Antiepileptics in the elderly. Pharmacoepidemiology and pharmacokinetics. *Arch. Fam. Med.* 3, 589–598 (1994).
3. GarrardJ, Cloyd J, Gross C *et al.*: Factors associated with antiepileptic drug use among elderly nursing home residents. *J. Gerontol. Med. Sci.* 55, M384–M392 (2000).
4. Lackner TE, Cloyd JC, Thomas LW, Leppik IE: Antidepressant drug use in nursing home residents: effects of age, gender, and comedication on patterns of use. *Epilepsia* 39, 1083–1087 (1998).
5. Garrard J, Harms S, Hardie N *et al.*: Antiepileptic drug use in nursing home admissions. *Ann. Neurol.* 54, 75–85 (2003).

• **AEDs are commonly used in older people in nursing facilities for treatment of epilepsy and other disorders.**

6. Rogawski MA, Loscher W: The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions. *Nature Medicine* 10, 685–692 (2004).
7. Gilliam FG, Fessler AJ, Baker G *et al.*: Systematic screening allows reduction of adverse epileptic drug effects: a randomized trial. *Neurology* 62, 23–27 (2004).
8. Ramsay RE, Rowan AJ, Pryor FM: Special considerations in treating the elderly patient with epilepsy. *Neurology* 62(Suppl. 2) S24–S29 (2004).
9. Young GB, Oppenheimer SR, Gordon BA *et al.*: Ataxia in institutionalized patients with epilepsy. *Can. J. Neurol. Sci.* 21, 252–258 (1994).
10. Kleopa K, Jacobsen M: Gait disorders in elderly patients with idiopathic generalized epilepsy. *Epilepsia* 39(Suppl. 6), 120 (1998).
11. Fife TD, Baloh RW: Disequilibrium of unknown cause in older people. *Ann. Neurol.* 34(5) 694–702 (1993).
12. Persson HB, Alberts KA, Farahmand BY, Tomson T: Risk of extremity fractures in adult out-patients with epilepsy. *Epilepsia* 43, 768–772 (2002).

• **Demonstrates that fractures are more common among those with epilepsy and more than half are related to falls or accidents unrelated to seizures.**

13. Mattson RH, Gidal BE: Fractures, epilepsy, and antiepileptic drugs. *Epilepsy Behav.* 5(Suppl. 2), S36–S40 (2004).
14. Ensrud KE, Walczak TS, Blackwell T *et al.*: Antiepileptic drug use increases rates of bone loss in older women: a prospective study. *Neurology* 62, 2051–2057 (2004).
15. Bohannon AD, Hanlon JT, Landerman R, Gold DT: Association of race and other potential risk factors with nonvertebral fractures in community-dwelling elderly women. *Am. J. Epidemiol.* 149, 1002–1009 (1999).
16. Shill HA, Fife TD: Valproic acid toxicity mimicking multiple system atrophy. *Neurology* 55, 1936–1937 (2000).
17. Specht U, May TW, Rohde M *et al.*: Cerebellar atrophy decreases the threshold of carbamazepine toxicity in patients with chronic focal epilepsy. *Arch. Neurol.* 54(4) 427–431 (1997).
18. Torvik A, Torp S, Lindboe CF: Atrophy of the cerebellar vermis in aging: a morphometric and histologic study. *J. Neurol. Sci.* 76, 283–294 (1986).
19. Raz N, Torres IJ, Spencer WD *et al.*: Age-related regional differences in cerebellar vermis observed *in vivo*. *Arch. Neurol.* 49, 412–416 (1992).
20. Ney GC, Lantos G, Barr WB, Schaul N: Cerebellar atrophy in patients with long-term phenytoin exposure and epilepsy. *Arch. Neurol.* 51, 767–771 (1994).
21. Kokenge R, Kutt H, McDowell F: Neurological sequelae following Dilantin overdose in a patient and in experimental animals. *Neurology* 15, 823–829 (1965).
22. Arima K, Kitamura J, Onuma T, Hirose H, Yamadera H, Yamaguchi A: Analysis of swaying of center of gravity in standing posture of patients with antiepileptic drugs. *Jpn. J. Psych. Neurol.* 44, 371–373 (1990).

• **An attempt to quantify balance effects in patients taking AEDs, which finds greater imbalance in patients on more than one AED.**

23. Patat A, Foulhoux P: Effect on postural sway of various benzodiazepine tranquillizers. *Br. J. Clin. Pharmacol.* 20, 9–16 (1985).
24. Noachtar S, von Maydell B, Fuhry L, Buttner U: Gabapentin and carbamazepine affect eye movements and posture control differently: a placebo-controlled investigation of acute CNS side effects in healthy volunteers. *Epilepsy Res.* 31, 47–57 (1998).
25. Delcker A, Wilhelm H, Timmann D, Diener HC: Side effects from increased doses of carbamazepine on neuropsychological and posturographic parameters of humans. *Eur. Neuropsychopharmacol.* 7, 213–218 (1997).
26. Bruni J: Outcome evaluation of gabapentin as add-on therapy for partial seizures. 'NEON' Study Investigators Group. Neurontin Evaluation of Outcomes in Neurological Practice. *Can. J. Neurol. Sci.* 25, 134–140 (1998).
27. Sivenius J, Kalvaiainen R, Ylinen A, Riekkinen P: Double-blind study of gabapentin in the treatment of partial seizures. *Epilepsia* 32, 539–542 (1991).
28. Fisher RS, Sachdeo RC, Pellock J *et al.*: Rapid initiation of gabapentin: a randomized, controlled trial. *Neurology* 56, 743–748 (2001).
29. Parsons B, Tive L, Huang S: Gabapentin: a pooled analysis of adverse events from three clinical trials in patients with postherpetic neuralgia. *Am. J. Ger. Pharmacol.* 2, 157–162 (2004).
30. Marson AG, Kadir ZA, Hutton JL, Chadwick DW: The new antiepileptic drugs: a systematic review of their efficacy and tolerability. *Epilepsia*, 38, 859–880 (1997).

•• **Thorough meta-analysis of efficacy and adverse effects showing no substantive differences among AEDs in their affect on balance, but finding increased balance effects with all drugs compared with placebo.**

31. Curran MP, Wagstaff AJ: Gabapentin: in postherpetic neuralgia. *CNS Drugs* 17(13), 975–982 (2003).
32. Singh D, Kennedy DH: The use of gabapentin for the treatment of postherpetic neuralgia. *Clinical Ther.* 25, 852–889 (2003).
33. Matsuo F, Bergen D, Faught E *et al.*: Placebo-controlled study of the efficacy and safety of lamotrigine in patients with partial seizures. US Lamotrigine Protocol 05 Clinical Trial Group. *Neurology* 43, 2284–2291 (1993).
34. Messenheimer J, Ramsay RE, Willmore LJ *et al.*: Lamotrigine therapy for partial seizures: a multicenter, placebo-controlled, double-blind, crossover study. *Epilepsia* 35, 113–121 (1994).
35. Ramaratnam S, Marson AG, Baker GA: Lamotrigine add-on for drug-resistant partial epilepsy. *Cochrane Database of Systematic Reviews*; 3:CD001909 (2001).
36. Faught E, Matsuo FU, Schachter S, Messenheimer J, Womble GP: Long-term tolerability of lamotrigine: data from a 6-year continuation study. *Epilepsy Behav.* 5, 31–36 (2004).
37. Collaborative Group for Epidemiology of Epilepsy: Adverse reactions to antiepileptic drugs: a multicenter survey of clinical practice. *Epilepsia* 27, 323–330 (1986).
38. Iivanainen M: Phenytoin: effective but insidious therapy for epilepsy in people with intellectual disability. *J. Intellect. Disabil. Res.* 42 (Suppl. 1), 24–31 (1998).

39. Ben-Menachem E, Henrisksen O, Dam M *et al.*: Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial seizures. *Epilepsia* 37, 539–543 (1996).
40. Faught E, Wilder BJ, Ramsay RE *et al.*: Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages. Topiramate YD Study Group. *Neurology* 46, 1684-1690 (1996).
41. Privitera M, Fincham R, Penry J *et al.*: Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 600-, 800- and 1,000-mg daily dosages. Topiramate YE Study Group. *Neurology* 46, 1678–1683 (1996).
42. Sharief M, Viteri C, Ben-Menachem E *et al.*: Double-blind, placebo-controlled study of topiramate in patients with refractory partial epilepsy. *Epilepsy Res.* 25, 217–224 (1996).
43. Tassinari CA, Michelucci R, Chauvel P *et al.*: Double-blind, placebo-controlled trial of topiramate (600 mg daily) for treatment of refractory partial epilepsy. *Epilepsia* 37, 763–768 (1996).
44. Beydoun A, Sachdeo RC, Kutluay E, McCague K, D'Souza J: Sustained efficacy and long-term safety of oxcarbazepine: one-year open-label extension of a study in refractory partial epilepsy. *Epilepsia* 44, 1160–1165 (2003).
45. Kalis MM, Huff NA: Oxcarbazepine, an antiepileptic agent. *Clin. Therapeutics* 23, 680–700 (2001).
46. Sachdeo R, Beydoun A, Schachter S *et al.*: Oxcarbazepine (Trileptal) as monotherapy in patients with partial seizures. *Neurology* 57, 864–871 (2001).
47. Barcs G, Walker EB, Elger CE *et al:* Oxcarbazepine placebo-controlled, dose-ranging trial in refractory partial epilepsy. *Epilepsia* 41, 1597–1607 (2000).
48. Kutuluay E, McCague K, D'Souza J, Beydoun A: Safety and tolerability of oxcarbazepine in elderly patients with epilepsy. *Epilepsy Behav.* 4, 175–180 (2003).
49. Chadwick DW, Marson AG: Zonisamide add-on for drug-resistant partial epilepsy. *Cochrane Database of Systematic Reviews* 2, CD001416 (2002).
50. Brodie MJ, Duncan R, Vespignani H, Solyom A, Bitenskyy V, Lucas C: Dose-dependent safety and efficacy of zonisamide: a randomized, double-blind, placebo-controlled study in patients with refractory partial seizures. *Epilepsia* 46, 31–41 (2005).
51. Brodie MJ: Zonisamide clinical trials: European experience. *Seizure* 13(Suppl. 1), S66–S70 (2004).
52. Sackellares JC, Ramsay RE, Wilder BJ, Browne TR 3rd, Shellenberger MK: Randomized, controlled clinical trial of zonisamide as adjunctive treatment for refractory partial seizures. *Epilepsia* 45, 610–617 (2004).
53. Ferrendelli JA, French J, Leppik I *et al.*: Use of levetiracetam in a population of patients aged 65 years and older: a subset analysis of the KEEPER trial. *Epilepsy Behav.* 4, 702–709 (2003).
54. Salas-Puig J, Serratosa JM, Viteri C, Gil-Nagel-Rein A: Grupo Espanol del Estudio SKATE. *Rev. Neurologica* 38, 1117–1122 (2004).
55. Cramer JA, Leppik IE, Rue KD, Edrich P, Kramer G: Tolerability of levetiracetam in elderly patients with CNS disorders. *Epilepsy Res.* 56, 135–145 (2003).
- **Report on levetiracetam in older people. Found that dizziness was the most common reason patients stopped the drug but that the incidence was still quite low. Suggested that levetiracetam may be a good choice of an AED for older people due to its favorable side effect profile.**
56. Pereira J, Marson AG, Hutton JL: Tiagabine add-on for drug-resistant partial epilepsy. *Cochrane Database of Systematic Reviews* 3, CD001908 (2002).
57. Crawford P, Meinardi H, Brown S *et al.*: Tiagabine: efficacy and safety in adjunctive treatment of partial seizures. *Epilepsia* 42, 531–538 (2001).
58. Mattson RH, Cramer JA, Collins JF *et al.*: Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *N. Engl. J. Med.* 313, 145–151 (1985).
59. Munoz-Garcia D, Del Ser T, Bermejo F, Portera A: Truncal ataxia in chronic anticonvulsant treatment. Association with drug-induced folate deficiency. *J. Neurol. Sci.* 55, 305–311 (1982).
60. Klein-Schwartz W, Shepherd JG, Gorman S, Dahl B: Characterization of gabapentin overdose using a poison center case series. *J. Toxicol. Clin. Toxicol.* 41, 11–15 (2003).
61. Curtis DL, Piibe R, Ellenhorn MJ, Wasserberger J, Ordog G: Phenytoin toxicity: a review of 94 cases. *Vet. Hum. Toxicol.* 31, 164–165 (1989).
62. Hwang WJ, Tsai JJ: Acute phenytoin intoxication: causes, symptoms, misdiagnoses, and outcomes. *Kaohsiung J. Med. Sci.* 20, 580–585 (2004).
63. Schmidt S, Schmitz-Buhl M: Signs and symptoms of carbamazepine overdose. *J. Neurol.* 242, 169–173 (1995).
64. Chadwick DW, Anhut H, Greiner MJ *et al.*: A double-blind trial of gabapentin monotherapy for newly diagnosed partial seizures. International Gabapentin Monotherapy Study Group 945–77. *Neurology* 51, 1282–1288 (1998).
65. Brodie MJ, Overstall PW, Giorgi L: Multicentre, double-blind, radomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. *Epilepsy Res.* 37, 81–87 (1999).
66. Steiner TJ, Dellaportes CL, Findley LJ *et al.*: Lamotrigine monotherapy in newly diagnosed untreated epilepsy: a double-blind comparison with phenytoin. *Epilepsia* 40, 601–607 (1999).
- **Placebo-controlled blinded study which found that lamotrigine caused less ataxia than phenytoin.**
67. Privitera MD, Brodie MJ, Mattson RH, Chadwick DW, Neto W, Wang S: Topiramate, carbamazepine and valproate monotherapy: double-blind comparison in newly diagnosed epilepsy. *Acta Neurol. Scand.* 107, 165–175 (2003).
68. Fife TD, Fisher RS, Blum D: Measuring the effects of antiepileptic medications on balance in older people. *International Geriatric Epilepsy Symposium*, Miami, Florida, USA (2003).
69. Bill PA, Vigonius U, Pohlmann H *et al.*: A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy. *Epilepsy Res.* 27, 195–204 (1997).
70. Christe W, Kramer G, Vigonius U *et al.*: A double-blind controlled clinical trial: oxcarbazepine versus sodium valproate in adults with newly diagnosed epilepsy. *Epilepsy Res.* 26, 451–460 (1997).
71. Dam M, Ekberg R, Loyning Y *et al.*: A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed previously untreated epilepsy. *Epilepsy Res.* 3, 70–76 (1989).
72. Gilliam F, Vasquez B, Sackellares JC *et al.*: An active-control trial of lamotrigine monotherapy for partial seizures. *Neurology* 51, 1018–1025 (1998).
73. Rowan AJ, Ramsay RE, Collins JF *et al.*: New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. *Neurology* 64, 1868–1873 (2005).
74. Karceski S, Morrell M, Carpenter D: The Expert Consensus Guideline Series: Treatment of Epilepsy. *Epilepsy Behav.* 2(Suppl. 6), A1–A50 (2001).
- **Consensus statement favoring lamotrigine, gabapentin, oxcarbazepine and carbamazepine over phenobarbital and phenytoin due to fewer adverse effects, including dizziness and ataxia.**