Professor Terence O’Brien considers evidence for the impacts of prolonged use of epilepsy medication.

There is no cure for epilepsy, and most people require treatment with antiepileptic drugs (AEDs) for many years. Often these people ask “what effects will taking these drugs for years have on my body?”

Overall AEDs are extremely safe for long-term use, but long-term treatment can have consequences in some patients, and these have been the subject of recent attention by researchers.

If you’ve been taking epilepsy medication for a long time, learning about these impacts is your first step to addressing them and giving yourself the greatest chance to enjoy the best possible quality of life.

Effects to be aware of

There are a number of adverse health effects that can occur in some patients with long-term treatment. In summary, they are:

1. Metabolic effects
   a Bone Health:
      Decreased bone density
      Increased fracture risk
   b Weight Changes:
      Cardiovascular implications
**Sex hormone effects:**
- Polycystic ovaries

2. **Neurological (Brain)**
3. **Dermatological (Skin)**
4. **Haematological (Blood)**

- My discussion here covers topics of recent research interest: metabolic and neurological effects, and bone health and increased fractures. I’ll also touch on the effects of AEDs on weight, and sexual hormones and fertility.

### Fracture risk

AED users have increased risk of fracture, evidenced from a number of well-controlled studies. One of the largest and most thorough is a case-control study from the UK involving over 230,000 patients. Taking an AED was the single greatest risk factor for fractures of all the medication types. Fracture risk increased by 2.1 times for AED users.

Another more recent large study confirms that fracture rates are twice as high among the epilepsy population. However, the authors pointed out that further studies are needed to clarify whether this results from the disease, or the AED use, or a combination of both.

This is a serious health issue particularly as AEDs are now increasingly prescribed for conditions other than epilepsy, such as psychiatric conditions and chronic pain, which also require years spent on the same medication. Morbidity from a fracture is very high and 50% of people who have a hip fracture never fully recover.

The reason why patients taking AEDs experience increased fractures is likely to be multi-factorial (see Figure 1).

Bone disease is probably one factor, as well as an increased risk of falls from balance impairments, and also trauma during seizures. Several studies, which have documented the reason for fractures in patients with epilepsy, have provided evidence that fractures during seizures are unlikely to be the major reason that people with epilepsy have increased fracture risk.

### Bone health and bone fragility

Concerns about bone health and AEDs dates back to the 1960s when chronic AED use was implicated in rickets, osteoporosis and increased fracture risk. However these early studies were heavily biased to subjects who were chronically disabled or institutionalised. This meant they didn’t have exposure to as much sunlight or exercise and often smoked heavily, factors strongly influencing bone health. So many neurologists didn’t believe the results of these studies were relevant to otherwise healthy, mobile patients with epilepsy.

This was apparent when a 2001 US survey revealed very few neurologists screened their patients with epilepsy for bone disease, and less than 20% even mentioned the issue to their patients. In many countries like Australia, there’s no funding for bone density screening. (Interestingly, though, rebates are offered to Australians taking corticosteroids, which have been associated with significantly lower increases in osteoporosis and fracture risk than AEDs.)

In the 2005 paper1 published in *Neurology* from our group – led by Sandra Petty and John Wark from the Department of Medicine, The Royal Melbourne Hospital and The University of Melbourne – a matched twin-sibling design was used to address the issue of long-term AED use and bone health. This study compared the bone health of a person with epilepsy exposed to AEDs to their twin (or a sibling within three years of age of the same sex and same menopausal status) who had not been taking the medication. Twins and siblings share many of the genes and environmental factors that affect bone health, and therefore this study design is very powerful for enabling an examination of the specific effect of use of AEDs.

In this study, we found AED users had 6% reduced bone density at relevant sites for fractures (i.e. hip and forearm) compared to non-users. But when we considered specific risk groups – for example older age groups, people using drugs for more than two years or using drugs which affect vitamin D metabolism (such as carbamazepine or phenytoin) – we noticed up to 16% difference; particularly if risk factors existed concurrently.

When we look at the individual twin pair data, there seems to be population of people who are particularly vulnerable to the effects of AEDs on bone health, probably due to genetics and being predisposed to bone conditions.

In another more recent study from Sandra Petty and our group that examined pre- and post-menopausal women, menopausal status was demonstrated to be a less important factor in reduced bone density than length of time taking the drug. The longer the use, the higher the likelihood of reduced bone density if you’re genetically predisposed.

### What about balance?

Many people with epilepsy complain of balance disturbances. A study published by the Mayo Clinic, USA2, looked at the proportion of patients participating in AED trials who complained of balance problems. Overall, complaints about balance deficit increased two times for those who were taking AEDs compared to those taking placebo medication.

Until recently virtually no studies have looked objectively at the issue of the effect of long-term AED use and balance. Therefore we revisited our twin-sibling population1 examining this issue using a similar approach we had taken with bone health. Fall risk is not only a matter of balance. A number of factors contribute – how active you are; your muscle strength; balance function; and also your stride, gait and mobility.

The data was striking. We found that...

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**Aetiology of increased fracture risk in epilepsy - Figure 1**

- **Bone Disease**
- **Fractures During Seizures**
- **Likely Multifactorial**
- **Falls / Balance Impairment**
- ?? Other Factors e.g. Muscle weakness, neuropathy
Additional note: AEDs and pregnancy

Over 93% of women with epilepsy can expect to have normal pregnancies and healthy babies. Babies exposed to AEDs in utero have a 2-3 times higher than average risk of birth defects. Some AEDs and dosages have been associated with higher risks of birth defects. Since medication is important to prevent potential harm from uncontrolled seizures to mother and baby, patients should discuss the issue with their neurologist – preferably before becoming pregnant – to make any necessary medication changes before conception.

chronic AED users have significantly worse balance than their twin-sibling pairs. Balance function in AED users was effectively equivalent to someone 20 years older who had not been taking medication. In other words, a 50-year-old would have balance equivalent to a 70-year-old.

Specific risk factors for poor balance were:
- Taking more than one AED (polytherapy).
- Length of time on medication – the longer the duration, the worse the balance.
- Recent falls – poorer balance was more likely among people who had a fall in the previous year.

The first two factors were the most important in balance function.

Another consideration is whether long-term AED use causes cerebellar degeneration. The cerebellum at the base of the brain is central to balance function. One reason put forward for poorer balance of chronic AED users is the association between long-term phenytoin (Dilantin) and reduced cerebellum size.

One study I was involved with 10 years ago at the US Mayo Clinic¹ found that people with temporal lobe epilepsy had significantly smaller cerebellums. The longer the patients had epilepsy – meaning longer AED use – was significantly associated with this occurrence.

Body weight changes

Weight changes are more than just a cosmetic concern, they are an important health issue. A number of AEDs are associated with weight gain, especially sodium valproate (Epilim), but also carbamazepine (Tegretol), gabapentin (Neurontin) and pregabalin (Lyrica).

In contrast, some other medications are associated with weight loss, including topiramate (Topamax), while others like levitiracetam (Keppra) and lamotrigine (Lamictal) are weight neutral.

Concern about weight gain from sodium valproate is the most common cause for people stopping or being non-compliant with this AED, which is the most effective medication for the treatment of primary generalised epilepsy. Up to 40% of patients treated with valproate gain at least 5.5kg. There is evidence weight not only increases overall, but the proportion of abdominal fat increases. This is of particular concern because it is related to an increased risk of cardiovascular disease.

Studies in people with epilepsy have shown a greater waist to hip ratio – predictive of cardiovascular disease – in people taking sodium valproate, and there is close to two times increased risk of ischaemic heart disease.

Polycystic ovaries

There has been a lot of concern in medical literature regarding a potential association of chronic valproate use and Polycystic Ovary Syndrome (PCOS). This is a medical syndrome in which women have multiple cysts on their ovaries with an increase in circulating male sex hormones (androgens), obesity, insulin resistance and elevated levels of insulin.

However polycystic ovaries in isolation, without the hormonal abnormalities of PCOS, are a common finding in normal women. Up to 20% of women in the general community will have polycystic ovaries on ultrasound, and this becomes more common as women gain weight. However, whether there is a specific association between sodium valproate and PCOS (independent from its weight-gain effect) is still highly controversial.


What can we do?

Overall AEDs are very safe medications in long-term use, but we now know they have associated health issues in some patients. So we need to monitor for them, and reduce their occurrence in the future.

To address the increased risk of bone disease, falls and fractures:

1. Be aware – education about the issues is needed for patients, health professionals and support organisations so we can take measures to prevent the consequences.

2. Maintain good bone hygiene – through adequate diet, exercise, sun exposure and no smoking.

3. Monitor your vitamin D levels – particularly if you live in cooler and darker places like Melbourne in the winter where sun exposure is limited. Consider a vitamin D supplement.

4. Have periodical bone mineral density assessments – there is a good case for monitoring your bone health although these tests are not currently funded for AED users.

5. Improve your balance – there are a range of ways to address the functional effects on balance of AED use, for example attending a balance training clinic, or seeking physiotherapy or occupational therapy.

To prevent increases in abdominal fat and cardiovascular risk:

1. Be mindful of cardiovascular risk – don’t smoke, and watch your weight and your cholesterol levels. Improve your diet, fitness and consider changing to a medication with a different effect on weight.

2. Researchers need to explore mechanisms and risk factors (individual or drug specific) – a better understanding of how these problems occur should be a focus of research since it will be a long time before there is a cure for epilepsy and people must take AEDs for many years.

This article is based on a presentation by neurologist Professor Terence O’Brien, who is a leading researcher, clinician and educator from the Royal Melbourne Hospital and the University of Melbourne specialising in epilepsy treatment and imaging. He is also a 2010 committee member of the Epilepsy Society of Australia.