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EMAS position statement: Managing the menopause in women with epilepsy

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ABSTRACT

Introduction: Epilepsy is a major public health problem worldwide which is clinically characterized by recurrent seizures.
Aim: The aim of this position statement is to provide evidence-based advice on management of the menopause in postmenopausal women derived from the limited data available.
Materials and methods: Literature review and consensus of expert opinion.
Results and conclusions: Women with epilepsy may undergo an earlier natural menopause, between 3 and 5 years depending on seizure frequency, but the data are limited. Data regarding the effects of the perimenopause and menopause on epilepsy are conflicting: some studies show an increased risk of seizures but others do not. With regard to hormone therapy (HT) one study has shown an increase in seizures with oral therapy with conjugated equine estrogens and medroxyprogesterone acetate, but no data are available for other regimens. Women starting HT should be closely monitored as their antiepileptic drug (AED) needs may change. As vitamin D and calcium metabolism can be affected by AEDS, supplements should be considered. Herbal preparations should be avoided as their efficacy is uncertain and they may interact with AEDs.

1. Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent seizures, which may vary from a brief lapse of attention or muscle jerks, to severe and prolonged convulsions. Epilepsy is a major public health problem worldwide and fifty million people are thought to be affected [1]. The prevalence of epilepsy increases with age [2,3]. It increases from 90 per 100,000 people of age 65–70 years to 150 per 100,000 in those older than 80 years. In the elderly common causes of the first epileptic seizure include cerebrovascular disease, non-vascular dementias and neoplasms. The treatment goals are suppression and prevention of seizures. For these purposes, antiepileptic drugs (AEDs) are used. While most AEDs (carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and topiramate) may induce the cytochrome P450 isoenzyme 3A4, some (lamotrigine, sulthiame) may not [4]. Therefore, certain AEDs may accelerate hepatic metabolism of hormonal preparations and decrease serum concentrations of bioactive sex steroids.

Endogenous and exogenous sex steroids will affect seizure activity and epilepsy in women [4–6]. Estrogen can be a very potent proconvulsant, whereas progesterone can be anticonvulsant. The latter effect seems to be medicated via allopregnanolone, a metabolite of progesterone. Women may therefore have changes in seizure threshold related to their menstrual cycle and at the menopause [5,6]. However, data regarding the effect of the perimenopause and menopause on epilepsy are scant and conflicting [7–11]. Some studies show an increased risk of seizures but others do not. It is important to note that women with epilepsy may undergo an earlier natural menopause, between 3 and 5 years depending on seizure frequency, but again the data are limited [12,13].

2. Chronic conditions affecting postmenopausal women after the menopause

The commonest cause of death in women is cardiovascular disease and prevalence increases with age. Women with epilepsy may be at increased risk of cardiovascular disease due to AEDs such as valproate and the ketogenic diet which modify lipid metabolism [14]. Another major concern is bone health as epilepsy increases the risks of falls and fracture. Bone mineral density is significantly reduced in women using AEDs [15,16]. Furthermore taking AEDS doubles the risk of hip fracture [17]. Also a case–control study from the U.K. General Practice Research Database found that the risk of fractures increased with cumulative duration of exposure to AEDs (p for trend < 0.001), with the strongest association for greater than 12 years of use: adjusted OR 4.15 (95% CI 2.71–6.34). Risk estimates were higher in women than in men. There was no difference

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between users of AEDs that induce and AEDs that do not induce the hepatic cytochrome P450 system. [18]. AEDs may impact bone health via multiple mechanisms [19–21]. For example cytochrome P450-inducing AEDs increase metabolism of vitamin D, leading to decreased intestinal calcium absorption and subsequent bone mobilization.

Sexual dysfunction is common at the menopause and may be exacerbated by epilepsy but the mechanisms are uncertain and may be related to use of enzyme-inducing AEDs [22].

3. Hormone therapy (HT) in women with epilepsy

Indications for hormone therapy (HT) are dealing with menopausal symptoms and conservation of bone mass and fracture prevention. As epilepsy is affected by sex steroids careful consideration must be given to the regimen used. However, the data are extremely limited [23,24]. The details of the only randomized trial double-blind, placebo-controlled trial are now described. This was undertaken in postmenopausal women with epilepsy, taking stable doses of AEDs, and within 10 years of their last menses. After a 3-month prospective baseline, subjects were randomized to placebo, Prempro (0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate or CEE/MPA) daily, or double-dose CEE/MPA daily for a 3-month treatment period. Twenty-one subjects were randomized after completing baseline. The subjects' ages ranged from 45 to 62 years (mean, 53 years), and the number of AEDs used ranged from none to three (median, one). Five (71%) of seven subjects taking double-dose CEE/MPA had a worsening seizure frequency of at least one seizure type, compared with four (50%) of eight taking single-dose CEE/MPA and one (17%) of six taking placebo ($p = 0.05$). An increase in seizure frequency of the subject's most severe seizure type was associated with increasing CEE/MPA dose ($p = 0.008$). An increase in complex partial seizure frequency also was associated with increasing CEE/MPA dose ($p = 0.05$). Two subjects taking lamotrigine had a decrease in lamotrigine levels of 25–30% while taking CEE/MPA. The authors concluded that CEE/MPA is associated with a dose-related increase in seizure frequency in postmenopausal women with epilepsy. CEE/MPA may decrease lamotrigine levels. There are no data with other regimens with different estrogens and progestogens or transdermal or vaginal administration. It is not known whether women with epilepsy need higher doses of estrogen or whether transdermal rather than oral therapy is preferred depending on their AED use. Based on the randomized trial it would be prudent to closely monitor women who start HT as their AED needs may change.

4. Non-estrogen based treatments

Non-estrogen based treatments are used to treat hot flushes and symptoms of urogenital atrophy. Drug interactions need to be carefully assessed before using pharmacotherapy. Interventions to consider include clonidine, selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs), gabapentin and vaginal lubricants and mosturisers [24]. While bisphosphonates will conserve bone mass there are little data in women with epilepsy and there are concerns about the safety of long term use [25,26]. As vitamin D and calcium metabolism can be affected by AEDS, supplements should be considered. Herbal preparations should be avoided as their efficacy is uncertain and they may interact with AEDs [27].

5. Summary recommendations

- Menopausal women with epilepsy need specialist care.
- The menopause may affect seizures but the data are conflicting.
- Epilepsy may advance the age of menopause.
- HT may affect seizures but the data are extremely limited.
- Women starting HT should be closely monitored as their AED needs may change.
- Calcium and vitamin D supplements should be considered.
- Herbal preparations should be avoided as their efficacy is uncertain and they may interact with AEDs.

Conflict of interests

None declared.

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Provenance

EMAS position statement.

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