Women with Epilepsy

A Practical Management Handbook

EDITED BY
Esther Bui and
Autumn M. Klein

CAMBRIDGE Medicine

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University Printing House, Cambridge CB2 8BS, United Kingdom

Cambridge University Press is part of the University of Cambridge.

It furthers the University's mission by disseminating knowledge in the pursuit of education, learning and research at the highest international levels of excellence.

www.cambridge.org
Information on this title: www.cambridge.org/9781107659889

First published 2014

Printed and bound in the United Kingdom by Clays Ltd, St Ives plc

A catalogue record for this publication is available from the British Library

Library of Congress Cataloging-in-Publication Data
Women with epilepsy (2014)
Women with epilepsy : a practical management handbook / edited by Esther Bui, Autumn Klein.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-107-65988-9 (Paperback)
I. Bui, Esther, editor of compilation. II. Klein, Autumn, editor of compilation. III. Title.
[DNLM: 1. Epilepsy. 2. Women's Health. WL 385]
RC372.3
616.85′30082–dc23 2013041804

ISBN 978-1-107-65988-9 Paperback

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Preface

This book began with a simple desire to create a practical, portable tool to help busy practitioners care for women with epilepsy. It was developed for neurologists, internists, obstetricians and gynecologists, family physicians, anesthetists, midwives, nurses, social workers, pharmacists, neonatologists, and all those who care for women with epilepsy. The diversity of our audience reflects the inherent multidisciplinary nature of this practice. Caring for women with epilepsy, especially during pregnancy, has challenges that many of us frequently feel ill-equipped to manage. Questions such as:

- How do hormones influence seizures, and how is this best managed?
- What is the teratogenicity of newer drugs such as topiramate or levetiracetam?
- What is the best form of birth control to use in women with epilepsy?
- How do I give my patient the best chance of seizure freedom during pregnancy?
- What factors can predict seizures in pregnancy?
- How do I manage seizures or status epilepticus in pregnancy especially during labor and delivery?
- Do hormone replacement therapies pose a risk for seizure exacerbation?

I still recall the many sleepless nights ruminating over whether I was providing the best possible care for these women. This culminated when a young pregnant patient of mine with epilepsy deteriorated into status epilepticus. The challenges of this, and many other cases, have catalyzed for me a strong desire to summarize key and critical concepts in the care of these women. I am grateful to have worked with world experts on these topics. They have successfully distilled key practice points and provided comprehensive basic science data, pregnancy registry data, and expert opinion to further enrich our understanding and ability to counsel patients. This book is designed as a quick, accessible, everyday, easy-to-use manual that puts the essentials of caring for women with epilepsy at one's fingertips.

On a very personal note, it is with a heavy heart that I conclude this preface with a tribute to Autumn Klein my co-editor. Autumn was a force to be reckoned with, one in a million, a unique person who had a remarkable ability to be on the leading edge of her own field and yet simultaneously filled with humility and a curiosity that easily engaged others to learn with her. Autumn and I mutually viewed this book to be a labor of love on a topic that we both were passionate about. We worked closely together over the past 2 years to bring this book to life. Autumn died in the Spring of 2013, before she could see the completion of this work. I know with certainty that she would have wanted to, as I do, dedicate this book to our daughters. To Cianna, know that despite all the awards, accolades, and tributes that your mother received, you were her greatest prize. To my own daughter Madelaine, this work and all others to follow would be meaningless without you. You are my own greatest life achievement. I want to thank my husband Carlo, who has tirelessly championed my hopes and dreams, my parents John and Ruth, who gave up their own dreams to allow me to follow mine, my brothers San, Mark, and Luke who lead a blazing trail for me to follow, and Nick Dunton at Cambridge University Press who recognized the potential in me.

Chapter 1

Epidemiology of women with epilepsy

Kristi A. McIntosh and Nathalie Jette

Key points:

- **Gender differences are observed in specific epilepsy syndromes**
- **Women with epilepsy (WWE) are at increased risk for depression, anxiety, sexual dysfunction, and infertility**
- **WWE of childbearing age encounter challenges associated with contraceptive therapy, pregnancy, and anticonvulsant use**
- **WWE during menopause face unique concerns related to hormone replacement therapy and osteoporosis**

Introduction

Epilepsy is one of the most common neurological conditions affecting men and women of all ages. In this chapter, we review the epidemiology of the epilepsies along with the epidemiology of comorbidity and special issues WWE encounter throughout their life.

Epidemiology of epilepsy

Fifty million individuals worldwide are estimated to have epilepsy at any given time [1]. Prevalence of epilepsy is defined as the number of persons with epilepsy in a specific population at one point in time, divided by the number of persons in that population and time. Incidence of epilepsy is defined as the number of new cases of epilepsy over a specified time period [1]. The reported incidence and prevalence of epilepsy varies widely between studies. Reasons for these estimated differences may include variations in the case ascertainment methods, the lack of accepted diagnostic criteria, the variations in the study location, and possible underreporting due to the stigma associated with epilepsy.

The overall prevalence of epilepsy is estimated to be between 5 and 10 cases per 1,000 persons, excluding febrile convulsions, single seizures, and inactive epilepsy [2–6], but the median lifetime prevalence of epilepsy has been reported to be as high as 15.4 per 1,000 (4.8–49.6) in rural areas and 10.3 per 1,000 (2.8–37.7) in urban areas of developing countries [3]. The prevalence of epilepsy is slightly higher in males than females in many door-to-door studies and record-review studies. Still, the difference in prevalence between the genders is very slight and usually not significant [1, 7]. However, some studies do report a gender difference in the epilepsy prevalence. For example, in a Danish study

Women with Epilepsy, ed. Esther Bui and Autumn Klein. Published by Cambridge University Press.

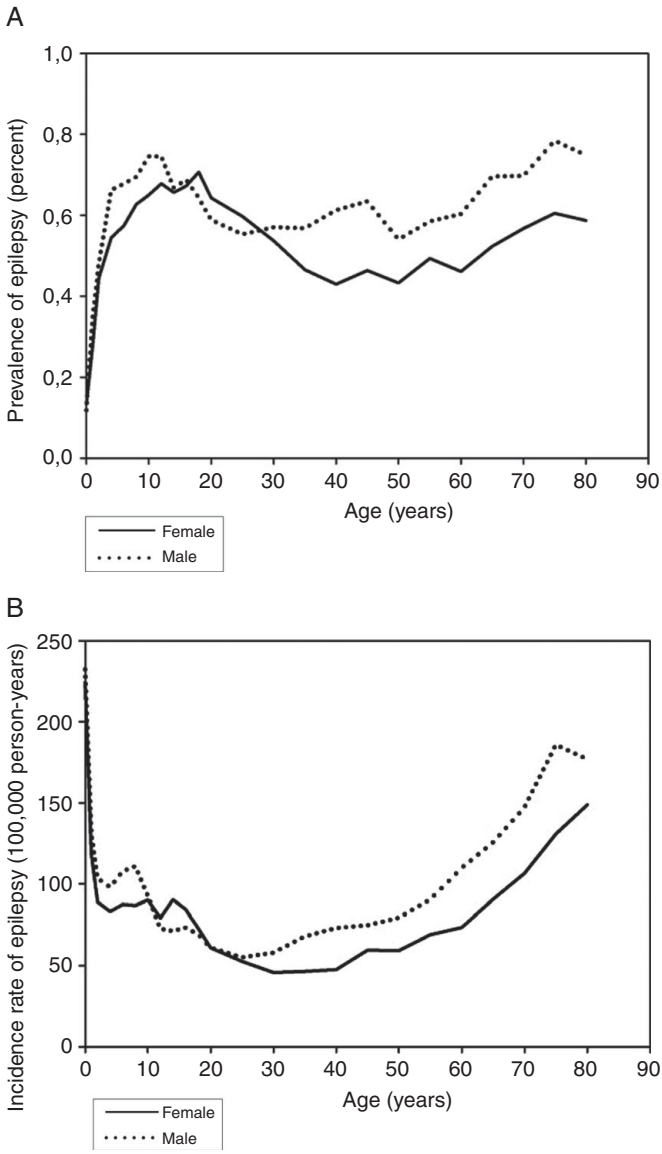

Figure 1.1: A: 5-year prevalence of epilepsy in Denmark. Estimates were based on 4,977,482 persons born in Denmark and resident in Denmark on December 31, 1999, including 28,303 diagnosed with epilepsy between 1995 and 1999. B: Age- and gender-specific incidence of epilepsy in Denmark. Estimates were based on 5,491,652 people born in Denmark followed up for development of epilepsy between 1995 and 2002, including 33,140 who developed epilepsy. The incidence measures the number of new cases per 100,000 person-years at risk. Reproduced with permission from Christensen et al. [2]

using population-based data from a national registry (Figure 1.1, A), the prevalence of epilepsy was higher in men compared to women for most age groups, except for the 16–25 year age group [2, 8]. In this study, men were also found to have higher incidence rates than women in all age categories with the exception of the 10–20 year age category (Figure 1.1, B) [2].

The overall incidence of epilepsy is usually reported to be about 40–70 cases per 100,000 person-years in developed countries, and about 100–190 cases per 100,000 person-years in developing countries [3, 7]. In a recent systematic review and meta-analysis, the median incidence of epilepsy was reported to be 45.0/100,000 person-years for high-income

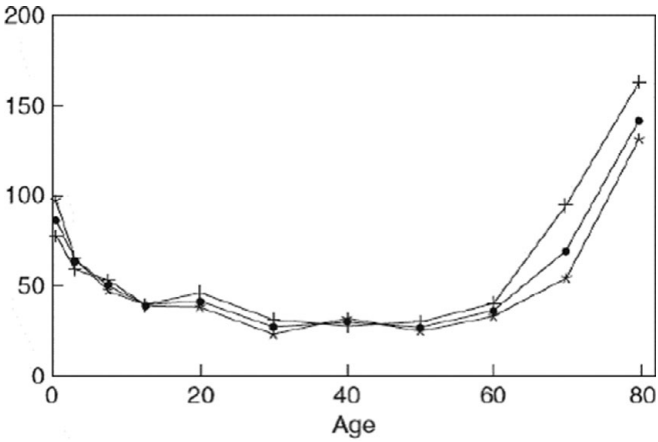

Figure 1.2: Age- and gender-specific incidence/100,000 of epilepsy in Rochester, Minnesota, 1935–1984. Total (solid circles), male (plus signs), female (stars). Reproduced with permission from Hauser et al. [10].

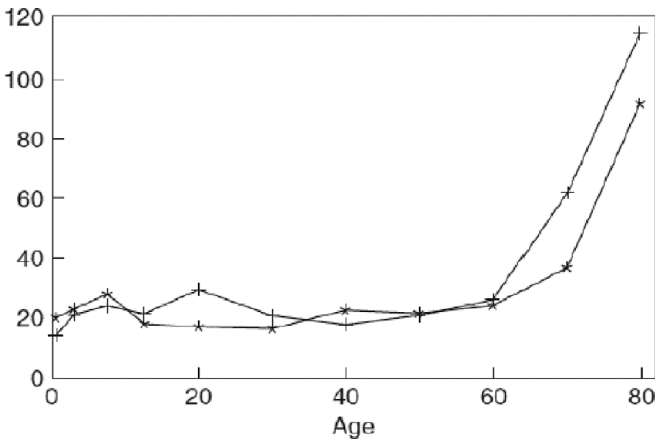

Figure 1.3: Age- and gender-specific incidence/100,000 of partial epilepsy in Rochester, Minnesota, 1935–1984. Male (plus signs), female (stars). Reproduced with permission from Hauser et al. [10].

countries and 81.7/100,000 person-years for low- and middle-income countries [9]. The incidence of epilepsy is often reported to have a bimodal distribution (Figure 1.2). It is highest in early childhood, lowest in early adult years, and then increases again after age 55 with the highest reported incidence in those over 75 years of age [10]. A similar pattern is described in both males and females.

The lifetime risk is the probability that a person will develop epilepsy over his or her lifetime. Based on calculations in a recent population-based study, 1 in 26 people will develop epilepsy during their lifetime, and men have a higher risk of developing epilepsy (1 of every 21 males) than women (1 of every 28 females) [11].

The causes behind these gender differences have not been elucidated. One hypothesis as to why epilepsy may be more common in men than in women is that men have a higher incidence of trauma-related disease, which in turn is associated with epilepsy. Focal epilepsy has also been found to occur more frequently among men than women (Figure 1.3). This higher incidence in men relative to women has not been reported in adolescents. This may be due to the higher incidence of primary generalized epilepsy (PGE) in

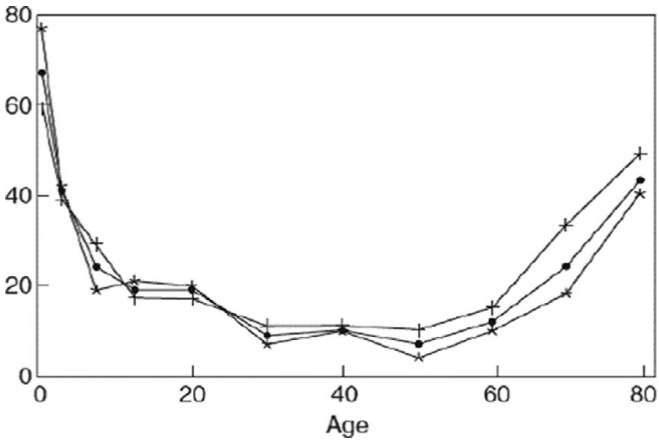

Figure 1.4: Age- and gender-specific incidence/100,000 of generalized onset epilepsy in Rochester, Minnesota, 1935–1984. Total (solid circles), male (plus signs), female (stars). Reproduced with permission from Hauser et al. [10].

women between the ages of 12 and 20 years (Figure 1.4). This increased incidence of generalized epilepsy in women relative to men in adolescence could be attributed to hormonal factors [8]. It has been hypothesized that sex hormones may contribute to the development of idiopathic generalized epilepsy in women, in which case this difference would be more obvious before menopause and decline with age, as demonstrated in the Danish study discussed above [8]. Furthermore, it has been suggested that higher reported estimates in males compared to females in many studies may be due to concealment of symptoms by women in certain cultures where women are considered "unmarriageable" if they have epilepsy [1].

Comorbidities

A number of mental health conditions are increased in persons with epilepsy compared to those without epilepsy [12]. Having epilepsy is also associated with a higher prevalence of somatic comorbidities compared to the general population [6, 13]. Here, we discuss gender differences in the epidemiology of mood and anxiety as well as sleep disorders in epilepsy. This is discussed in greater detail in Chapters 2 and 3.

Psychiatry

Mood disorders in epilepsy

Mood disorders are prevalent in those with epilepsy, with major depression being the most common mood disorder [14]. Recently, studies have shown that a history of major depression is associated with an increased risk for developing seizures and vice versa [15]. This two-way relationship suggests a possible shared pathogenetic origin [15].

Female gender is found to be associated with depression in those with or without epilepsy [14, 16]. Among women without epilepsy (WWoE), the prevalence of depressive mood disorders has been reported to be approximately two times higher in women than in men. In a nationally representative Canadian health survey using structured interviews for the assessment of major depressive disorder, depression was identified in 13% of those with epilepsy compared to 7% of those without epilepsy [14]. WWE were 2.6 times more

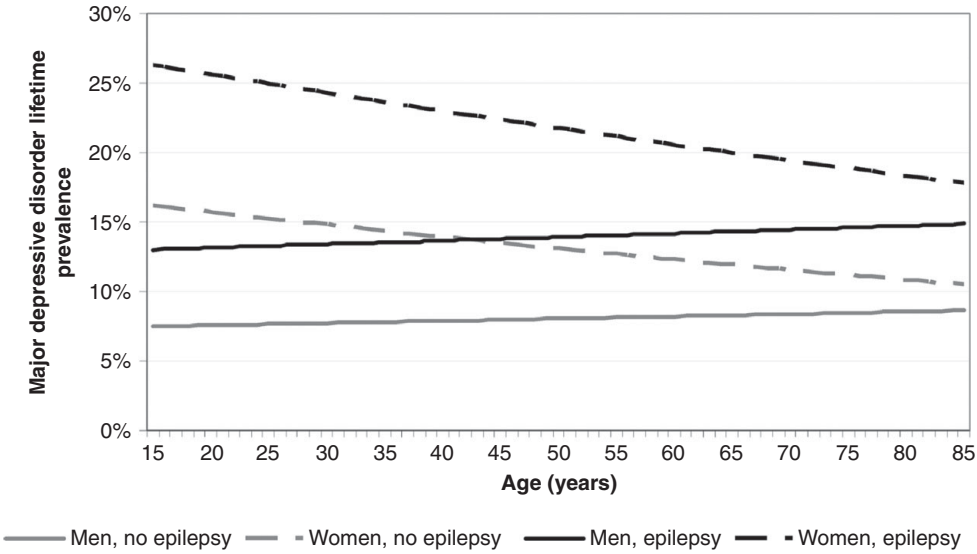

Figure 1.5: Logistic regression (fitted) models predicting the lifetime prevalence (proportion in percentage) of major depression disorder (on the y-axis) based on age (on the x-axis) and gender. Reproduced with permission from Tellez-Zenteno et al. [12].

likely (95% confidence intervals (CI), 1.6–4.3) to be depressed than men with epilepsy [14]. In another large Canadian population-based study using similar methodology, the odds of lifetime major depression was found to be higher in people with epilepsy compared to those without epilepsy [12]. The lifetime prevalence of major depressive disorder in those with epilepsy was 17.4% (95% CI, 10.0–24.9), compared to 10.7% (95% CI, 10.2–11.2) in those without epilepsy, with an odds ratio (OR) of 1.8 (95% CI, 1.0–3.1). In other population-based studies lifetime prevalence has been estimated to be as high as 30% [80]. Furthermore, the lifetime prevalence of major depressive disorders, while still increased for those with epilepsy has been shown to decline with age in women while remaining relatively stable in men (Figure 1.5) [12].

While no population-based studies have examined the incidence of postpartum depression (PPD) in WWE, smaller studies have reported an increased frequency of PPD in WWE compared to WWoE. For example, an Italian study of 55 postpartum women with and without epilepsy found that PPD occurred in 39% of WWE compared to 12% of WWoE ($p<0.05$) [17]. No specific causative factor, however, has been identified to explain this disparity.

Anxiety disorders

Whereas much is known about the association between epilepsy and depression, less is known about the epidemiology of anxiety disorders in those with epilepsy.

In a cross-sectional, population-based study from the UK using diagnoses from primary care records, anxiety disorders were reported in 11% of people with epilepsy ($n = 5,834$), compared to 5.6% of those without epilepsy ($n = 831,163$) [18]. The risk of anxiety was higher in both men and WWE compared to control, but higher in WWE overall. In the female 16–64 year age group, anxiety was reported in 14.2% of 2,338 WWE

compared to 7.5% of 410,851 WWoE (RR, 1.95; 95% CI, 1.8–2.2). In the 64 year and older age group, 9.0% of 642 WWE had anxiety compared to 7.8% of 118,516 WWoE (RR, 1.2; 95% CI, 0.9–1.5).

In a population-based Canadian health survey using structured interviews based on DSM-IV, those with epilepsy were more likely than those without epilepsy to report lifetime anxiety disorders with an OR of 2.4 (95% CI, 1.5–3.8). Of those with epilepsy, 12.8% (95% CI, 6.0–19.7) reported an anxiety disorder in the past 12 months compared to 4.6% (95% CI, 4.3–4.9) in the group without epilepsy. Similarly, 22.8% (95% CI, 14.8– 30.9) of those with epilepsy compared to 11.2% (95% CI, 10.8–11.7) of those without epilepsy reported a lifetime anxiety disorder. In both women and men with epilepsy, panic disorder and agoraphobia became more prevalent with age (and was found to be higher in women compared to men with epilepsy) but this was not found to occur in the general population [12].

Sleep

Sleep disturbances are reported more frequently in adults with epilepsy than in adults without epilepsy. Increasing evidence suggests that obstructive sleep apnea (OSA), excessive daytime sleepiness (EDS), and sleep maintenance insomnia (difficulty staying asleep) are more commonly found in adults with epilepsy than in those without [19–21]. However, population-based studies on sleep disturbances in patients with epilepsy are lacking. Furthermore, there has been little attention to gender differences in existing smaller studies.

In a mail survey of 1,183 Dutch outpatients, the 6-month prevalence of sleep disturbances in people with focal epilepsy was more than two times greater than that of healthy controls (38.6% vs. 18.0%) [22]. This was felt not to be due to any one particular type of sleep disturbance but rather all sleep disturbances were significantly more prevalent in the patients with epilepsy. A prospective Swiss study of 100 adult epilepsy patients found sleep complaints were three times as likely (30% vs. 10%) in a population of people with epilepsy compared with controls [21]. Of those with epilepsy, 52% were found to have sleep maintenance insomnia compared to 38% of controls [21]. In small case series, OSA has been reported in 10% of adults with epilepsy, 20% of children with epilepsy, and approaching 30% in drug-resistant epilepsy patients [19]. Furthermore, OSA is more likely to occur in those who are older, male, overweight, with drug-resistant or late onset epilepsy [19, 20].

More sleep problems are encountered by children with epilepsy than their healthy siblings and other healthy controls [20]. Gender does not appear to contribute to the frequency of problems with sleep in children [20].

Epilepsy in childhood and adolescence

Inheritance and genetics

Several factors have been found to be associated with a predisposition to epilepsy, particularly in families where one member is already affected. Affected children have a greater risk of being born to a mother with epilepsy (2.8–8.7%) compared to a father with epilepsy (1.0 to 3.6%) [23]. How early a parent developed epilepsy also predicts the likelihood of a child developing epilepsy [23]. A parent who develops epilepsy before age 20 has a 2.3–6% risk of their children developing epilepsy, while a parent who develops epilepsy after age 20 has a 1.0–3.6% risk of their children developing epilepsy [23]. Furthermore, in families who have both an affected parent and child, the risk of epilepsy for other siblings increases

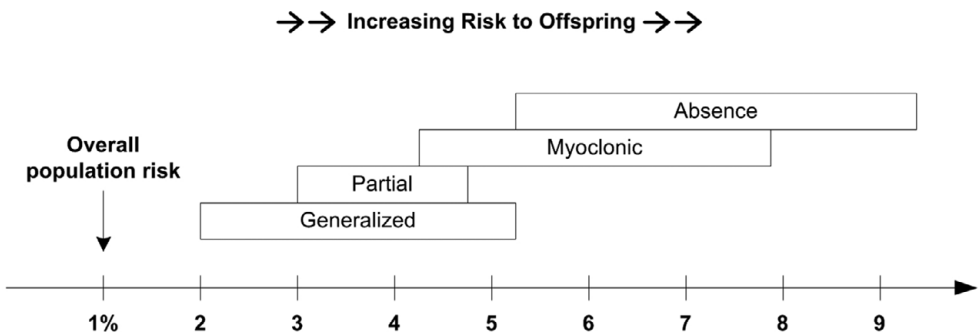

Figure 1.6: Percent of offspring affected with epilepsy. Reproduced with permission from Winawer and Shinnar [23].

from approximately 3% to 8% [23]. The epilepsy syndrome or seizure type also contributes to the likelihood of epilepsy developing in relatives. Occurrence of epilepsy in relatives is increased when the proband has idiopathic epilepsy with seizures such as myoclonic or absence seizures. In those with myoclonic seizures, a 4–8% risk of any epilepsy in offspring is seen, while in those with absence seizures, a 5–9% risk of any epilepsy is observed. The risk of epilepsy in those related to individuals with generalized epilepsy is greater than in those related to individuals with partial epilepsy in some studies; however this has not been observed in all studies (Figure 1.6) [23].

Epilepsy in girls and female adolescents

Gender differences have been identified in various epilepsy syndromes. Idiopathic generalized epilepsy, which accounts for 15–20% of the epilepsies, can be found more frequently in females than in males [24]. Childhood absence epilepsy (CAE) was reported in 2.5% of boys compared to 11.4% of girls in a Norwegian population-based study [25]. Juvenile absence epilepsy (JAE) and juvenile myoclonic epilepsy (JME) were found to be more common among females than males using data from 2,488 individuals with epilepsy from a Danish outpatient epilepsy clinic and the Danish Twin Registry [8]. JAE was 3 times more common in females than males (76% vs. 24%), whereas JME was 1.5 times more common in females than males (61% vs. 39%) [8]. However, there has been less agreement as to whether gender differences exist in localization-related epilepsies (LRE). While one prospective study of 996 patients with suspected seizures conducted over a 4-year period in Australia reported an equal gender distribution of hippocampal sclerosis (81% in men vs. 79% in women) [26], another retrospective study of 153 patients presenting for pre-surgical evaluation in Germany found that the expression of focal epilepsy due to mesial temporal sclerosis is not the same in females and in males [27]. Females were more likely to experience isolated auras than males (OR, 2.1; 95% CI, 1.1–4.2), and less likely to have secondary generalized seizures (OR, 0.44, 95% CI, 0.21–0.92). Furthermore, they also found that electrographic findings were more likely to be on the same side of hippocampal sclerosis in females compared to males (98% vs. 84%). Finally, specific hereditary epilepsy syndromes such as Rett syndrome, Aicardi syndrome, subcortical band heterotopia and epilepsy and mental retardation limited to females (EFMR) are seen primarily in females due to mutations identified in the X chromosome. These syndromes are discussed in detail in Chapter 6.

Catamenial epilepsy

Catamenial epilepsy is defined as a doubling in daily seizure frequency during specific phases of the menstrual cycle [28]. Three categories of catamenial seizure patterns have been described: perimenstrual (C1 pattern), periovulatory (C2 pattern), and entire second half of the cycle (Figure 8.1) in anovulatory cycles (C3 pattern) [28]. Population-based studies exploring the prevalence of catamenial epilepsy are lacking. However, a catamenial pattern was found in 39% of women with LRE in a prospective study of 87 women [29] and 31% of adolescent females in a prospective study of 42 WWE from an Egyptian pediatric neurology clinic [30]. Furthermore, the laterality and focality of epilepsy may play an important role in the ability for reproductive hormones to affect the seizure pattern during the monthly cycle [31].

Epilepsy in childbearing

Fertility and epilepsy

Sexual dysfunction

Population-based studies examining sexual dysfunction in WWE are lacking. However, smaller series have found that WWE are more likely to suffer from sexual dysfunction than WWoE. The epilepsy syndrome and its localization influence sexual function. An American study explored sexual dysfunction in 57 reproductive-aged women on antiepileptic drug (AED) monotherapy recruited from tertiary epilepsy centers compared to 17 WWoE. Lower scores for sexual dysfunction were found in women with primary generalized epilepsy (20.0%) and localization-related epilepsy (20.7%) compared to controls (9%) [32]. Furthermore, sexual dysfunction is seen more frequently in right than left temporal lobe epilepsy (TLE) in both men and women [33].

Another controlled prospective American study of 36 women with TLE recruited from a neurology outpatient service, and 12 controls recruited from the community, examined whether changes in sexual function were found more frequently in women with unilateral TLE [33]. Indeed, sexual function scores were substantially worse with right TLE than left TLE. Additionally, 50.0% of women with right TLE and 30.0% of women with left TLE had sexual dysfunction as compared with 8.3% of WWoE. However, these differences were only significant for those with right TLE [33]. Some AEDs, particularly older, enzyme-inducing AEDs, contribute to sexual dysfunction due to potential influences on the hypothalamic-pituitary-gonadal axis resulting in changes in the levels of hormones supporting sexual behavior (Chapter 9). Enzyme-inducing AEDs are believed to increase sex hormone-binding globulin and thereby decrease bioavailable testosterone which contributes to the emergence of sexual dysfunction [33]. While not statistically significant, 40.7% of WWE receiving AEDs reported increased sexual dysfunction compared to 33.3% of those not receiving AEDs in this same study [33].

Reproductive dysfunction

In WWE, menstrual cycle irregularities, increased risk of infertility, or signs of polycystic ovary syndrome (PCOS) are frequently encountered. Both seizures and AEDs have been causally implicated [34]. Some of the greatest challenges in comparing the results from studies looking at menstrual disorders in WWE are the lack of menstrual disorder definitions, and of population-based studies. Most published studies report data from highly selected, biased populations (e.g., women referred to a neuroendocrine clinic).

In a retrospective, questionnaire-based study of 265 WWE and 142 matched WWoE from three different Norwegian hospitals, menstrual disorders were significantly higher in WWE (48.0%) than in controls (30.7%) [35]. In another retrospective American analysis of 100 women with LRE, menstrual disorders were identified by 32% [36]. In a case-control study, 12/36 (33.3%) of WWE compared to 14/100 (14%) community-based WWoE ($p = 0.02$) had menstrual disorders (defined as "abnormal cycle interval, oligomenorrhea, polymenorrhea, increased variability of cycle interval or menometrorrhagia") [37].

Menstrual cycle irregularities, anovulation, higher androgen levels, carbohydrate intolerance with obesity, and polycystic-appearing ovaries are characteristics of PCOS. A lack of a standardized definition of PCOS could explain the varying reported rates in both women with and without epilepsy [38]. Once again, however, there is a lack of population-based studies examining the epidemiology of PCOS in WWE.

In a recent Finnish study examining reproductive endocrine function in 148 WWE, PCOS was found to occur in 28% of WWE, 52% of WWE on valproate (VPA), and 11% of controls. WWE on VPA were 5.46 times more likely to have PCOS when compared to controls (95% CI, 2.23–13.03) [39]. In a recent meta-analysis including 556 WWE treated with VPA, 593 women treated with other AEDs, 120 untreated WWE, and 329 healthy controls, the likelihood of developing PCOS was 1.95 times greater in VPA-treated WWE compared to other AED-treated women [38]. The possibility of developing features of PCOS in those treated with VPA seems to depend on the age at which the female was first treated with VPA [40]. In a prospective American study of 225 WWE taking VPA compared to 222 WWE taking lamotrigine (LTG), the occurrence of PCOS symptoms occurred more frequently in women started on VPA rather than LTG before the age of 26 years compared to WWE in whom VPA was started at the age of 26 years or older [40].

Another pattern of reproductive dysfunction described in patients with epilepsy is hypothalamic amenorrhea. This is one of the more severe yet common patterns of hypogonadotropic hypogonadism. In one study, 50 women with TLE referred for neurologic evaluation were studied, with 8 (16%) found to have amenorrhea. This is much higher than the expected frequency of 1.5% in the general population [41]. Furthermore, it has been found to occur more commonly in RTLE than LTLE [37, 42]. However, population-based estimates of amenorrhea in WWE have not yet been published.

There are, however, population-based data examining fertility rates in WWE between 1991 and 1995 compared to the 1993 population fertility rates for England and Wales [43]. The fertility rate in WWE aged 15–44 was 47.1 live births per 1,000 women per year (95% CI, 42.3–52.2), compared with a national rate of 62.6. The most significant decrease in fertility rates was among the WWE in the 25–39 year age group ($p<0{\cdot}001$). In a more recent, prospective cohort of 375 WWE enrolled in an epilepsy and pregnancy registry in India, 38% failed to conceive, with the most important predictors of infertility being multiple AEDs, older age, and lower education [44].

Lower birth rates may be due to lower marriage rates, reproductive dysfunction, fear of birth defects, and concern for an increased risk of epilepsy in the offspring [45]. In a population-based study of 19 American states, 55.5% (95% CI, 51.3–59.7) of those with epilepsy were married or in a common-law relationship compared to 64.1% (95% CI, 63.6–64.7) of those without epilepsy. Of those with epilepsy, 22.9% (95% CI, 20.0–26.2) were formerly married compared to 18.0% (95% CI, 17.6–18.3) of those without epilepsy. Finally, 21.5% (95% CI, 17.7–26.0) of those with epilepsy were never married compared to 17.9% (95% CI, 17.4–18.4) of those without epilepsy [6]. Similar findings have been

reported in an Indian study of 300 epilepsy patients. Of those with epilepsy (n = 300), 44.6% of women were never married compared to 22.3% of women in the general population (n = 4,687). Of those with epilepsy, 51.1% of women were married compared to 75.7% of women in the general population. Finally, 4.3% of WWE were divorced compared to 2% of women in the general population [46]. Fertility in WWE is discussed in further detail in Chapter 9.

Contraception and epilepsy

It is estimated that nearly half of all pregnancies among WWE are unplanned, similar to the frequency seen in the general population [79]. Contraceptive management in WWE is paramount, due to the possible maternal and fetal complications if contraception fails. Furthermore, the use of enzyme-inducing AEDs can result in birth control failure and contribute to the relatively high number of unplanned pregnancies in WWE [47, 48]. Therefore, preconception counseling to all WWE of childbearing age is necessary.

The prevalence of contraceptive use in 1,630 Dutch women of childbearing age on AEDs was calculated in a study using a population-based pharmaceutical dispensing database [49]. The authors found that only 34.3% of AED users were prescribed highly effective contraceptives compared with 41.2% of the general population of women of childbearing age ($p<.001$). They also found that of WWE who used enzyme-inducing AEDs in combination with a highly effective contraceptive method, 43.5% of them were on an oral contraceptive (OC) containing less than the recommended 50 μg of estrogen. These findings are consistent with a large, population-based study of childbearing WWE on AEDs in the UK. This latter study found that 16.7% of WWE were on OC, and of those on both an enzyme-inducing AED and an OC, 56% were on OC with an estrogen content less than 50 μg [50].

Despite the well-known effects of estrogen on lowering seizure threshold, an association between estrogen-containing OC and seizure exacerbation in WWE has not been seen. A large UK cohort study of 17,032 WWE followed for up to 26 years examined whether there was a relationship between OC use and an increase in the incidence of epilepsy or seizures [51]. No association was found between OC use and the development of epilepsy in WWoE or between OC use and seizure frequency in WWE.

Preconception counseling

There are no studies examining how common preconception counseling is for WWE. However, the use of preconception folic acid by WWE was reviewed by a committee assembled by the American Academy of Neurology (AAN) and American Epilepsy Society (AES) and is discussed below [52]. A prospective study of 970 pregnancies and 979 offspring in WWE reported a significant correlation between serum folic acid concentrations <4.4 nmol/L and malformations in newborns (adjusted OR, 5.8; 95% CI, 1.3–27) [53]. However, several other studies reviewed did not show a relationship between folic acid and major congenital malformations (MCMs), but were insufficiently powered to exclude a significant risk reduction from folic acid supplementation. Prevention of MCMs in offspring of WWE taking AEDs may occur with preconception folic acid supplementation.

The effectiveness of preconception folic acid supplementation was examined in a recent prospective, observational study by looking at the rate of MCMs in a group of women on AED monotherapy in the UK [54]. In the 1,935 cases that received

preconception folic acid, 76 MCMs (3.9%; 95% CI, 3.1–4.9) and 8 neural tube defects (NTDs) (0.4%; 95% CI, 0.2–0.8) were observed. There were 53 occurrences of a MCM (2.2%; 95% CI, 1.7–2.9) and 8 NTDs (0.34%; 95% CI, 0.2–0.7) in the 2,375 women who obtained folic acid but did not start taking it until later in the pregnancy (n = 1,825) or not at all (n = 550). Folic acid supplementation in this population of WWE was not associated with a reduction in the frequency of MCMs or NTDs. This study suggests that extrapolating findings from population-based studies of all pregnant women that took folate to groups of selected WWE enrolled in registries may be inappropriate. The higher risk of MCMs in WWE may be multifactorial and may also be explained by mechanisms other than those directly related to folic acid metabolism.

The evidence regarding the effectiveness of preconception counseling for WWE, calculated by a decrease in adverse pregnancy outcomes was recently published as a Cochrane review [55]. No studies met all study eligibility criteria. There is thus no strong evidence regarding the effectiveness of preconception counseling in decreasing adverse pregnancy outcomes for WWE and their offspring [56]. More population-based studies looking at folic acid intake in WWE and its benefits are required.

The prophylactic effect of folic acid supplementation on the likelihood of spontaneous abortion and pre-term delivery was examined prospectively in pregnant WWE on AEDs. These WWE were all registered in EURAP (an International Registry of AEDs and Pregnancy) at a single center, with 388 pregnancies in 244 patients investigated [57]. WWE that did not supplement with folic acid were more likely to have a spontaneous abortion than those who did supplement (OR, 2.6; 95% CI, 1.2–5.6). Consequently, pregnancies with folic acid supplementation were associated with a significant reduction of spontaneous abortion.

AEDs and fetal effects

The occurrence of fetal malformations is associated with the use of AEDs in pregnancy. Different AEDs are associated with different types of malformations in the offspring. Epilepsy and pregnancy registries exist to collect such information, as randomized clinical trials are difficult to conduct in pregnancy. Registries are found in many countries and differ in methodology and outcomes. Pharmaceutical companies may collect pregnancy data related to their product while other registries are driven by independent research groups who may collect and publish data on more than one AED for comparison [58]. Here, we primarily discuss population-based studies reporting on AEDs and the risk of MCMs. This is discussed further in Chapter 12.

One population-based retrospective study of WWE from Finland using data from the National Medical Birth Registry showed a higher risk of MCMs in the newborns of WWE exposed to any in utero AED (OR, 1.7; 95% CI, 1.1–2.8) compared to the newborns of WWE not exposed to AEDs. The likelihood of MCMs in infants exposed to in utero VPA monotherapy (OR, 4.2; 95% CI, 2.3–7.6) or polytherapy (OR, 3.5; 95% CI, 1.4–8.1) was also increased [59].

A systematic review and meta-analysis of international published registries examined the incidence of MCMs and other pregnancy outcomes after in utero AED exposure [60]. Fifty-nine studies involving 65,533 pregnancies in WWE and 1,817,024 in WWoE were included. The incidence of MCMs in offspring born to WWE was greater (7.1%; 95% CI, 5.6–8.5) compared to offspring born to WWoE (2.3%; 95% CI, 1.5–3.1). Incidence was

greatest for AED polytherapy (16.8%; 95% CI, 0.5–33.1). The highest MCMs' incidence rate belonged to VPA, at 10.7% (95% CI, 8.2–13.3) for monotherapy. VPA monotherapy and polytherapy drugs that included phenobarbital (PB), PHT, or VPA significantly increased the risk of MCMs in offspring exposed in utero.

A population-based cohort study of 837,795 infants born in Denmark investigated the relationship between in utero exposure to newer generation AEDs during the first trimester of pregnancy and the likelihood of developing MCMs [61]. Of the 1,532 infants exposed to LTG, oxcarbazepine (OXC), topiramate (TPM), gabapentin (GBP), or levetiracetam (LEV) during the first trimester, 3.2% were diagnosed with a MCM compared with 2.4% who were not exposed to an AED, with an adjusted OR of 1.0 (95% CI, 0.7–1.4). Of 1,019 AED-exposed newborns, a MCM was discovered in 38 (3.7%) exposed to LTG during the first trimester (OR, 1.2; 95% CI, 0.8–1.7), in 11 of 393 newborns (2.8%) exposed to OXC (OR, 0.9; 95% CI, 0.5–1.6), and in 5 of 108 newborns (4.6%) exposed to TPM (OR, 1.4; 95% CI, 0.6–3.6). Only 1 (1.7%) infant exposed to GBP (n = 59) and no infants exposed to LEV (n = 58) were diagnosed with MCMs, but the use of these AEDs is still less common in pregnancy.

There have also been studies examining the association between AED use and cognitive outcomes in children. A prospective, observational (non-population-based) study from epilepsy centers in the USA and the UK examined the cognitive effects of fetal exposure to AEDs in 309 children at 3 years of age [62]. Pregnant WWE were enrolled who were taking AED monotherapy (carbamazepine (CBZ), LTG, PHT, or VPA). Significantly lower IQ scores were found in 3-year-old children who had been exposed in utero to VPA compared to those children exposed to any other AEDs. After adjustment for maternal IQ, standardized AED dose in the mother, age of mother at delivery, gestational age of the neonate at delivery, and preconception folate supplementation, the mean IQ was 101 for children exposed to LTG, 99 for those exposed to PHT, 98 for those exposed to CBZ, and 92 for those exposed to VPA. A dose-dependent relationship between VPA use and IQ was noted.

An observational (non-population-based) study of WWE and their children was conducted through the Australian Pregnancy Register for WWE and Allied Disorders [63]. Researchers looked at the language skills of 102 school-aged children exposed prenatally to AEDs. With regards to mean language scores, children exposed to VPA monotherapy or polytherapy were significantly below normal, while children exposed to CBZ or LTG monotherapy, or polytherapy without VPA, were not. Additionally, first-trimester VPA usage resulted in a decrease in language scores.

Pregnancy and epilepsy

WWE have been found to have a higher risk of pregnancy and delivery complications. However, it is not clear if this is due to more severe epilepsy or the use of AEDs during pregnancy. A recent population-based study investigated whether pregnant WWE had a greater likelihood of complications during pregnancy and also explored the effects of AED use using databases on all births in Norway from 1999–2005 [64]. Main outcomes included pre-eclampsia, gestational hypertension, eclampsia, vaginal bleeding, and prematurity. WWE were more likely to have mild pre-eclampsia (OR, 1.3; 95% CI, 1.1–1.5) and delivery before week 34 (OR, 1.2; 95% CI, 1.0–1.5). WWE on AEDs were more likely to develop mild pre-eclampsia (OR, 1.8; 95% CI, 1.3–2.4), gestational

hypertension (OR, 1.5; 95% CI, 1.0–2.2), vaginal bleeding late in pregnancy (OR, 1.9; 95% CI, 1.1–3.2), and delivery before 34 weeks of gestation (OR, 1.5; 95% CI, 1.1–2.0) when compared to WWoE. However, these increased risks of complications were not seen in WWE not using AED.

A population-based study using the same databases as above including all births in Norway looked at whether WWE have a greater likelihood of complications during labor, and investigated the impact of AEDs [65]. Outcomes included induction, cesarean section, use of forceps and vacuum, abnormal presentation, placental abruption, mechanical disproportion, postpartum hemorrhage, atony, and decreased Apgar scores after 5 minutes. An elevated risk of induction (OR, 1.3; 95% CI, 1.1–1.4), cesarean section (OR, 1.4; 95% CI, 1.3–1.6), and postpartum hemorrhage (OR, 1.2; 95% CI, 1.1–1.4) were seen in WWE (on or off AEDs) compared with WWoE. However, even higher estimates were obtained in WWE on AEDs with ORs (95% CIs) of 1.6 (1.4–1.9), 1.6 (1.4–1.9), and 1.5 (1.3–1.9), respectively. The likelihood of an Apgar score less than 7 was higher in WWE on AEDs (OR, 1.6; 95% CI, 1.1–2.4) compared to WWoE. Only a mildly increased likelihood of cesarean delivery was found among WWE without AED compared to WWoE (OR, 1.3; 95% CI, 1.2–1.5). This is discussed further in Chapter 14.

Another recent population-based study investigated pregnancy, delivery, and MCM outcomes in WWE using data also collected from the compulsory Medical Birth Registry of Norway [66]. A surprising 66% of WWE did not use AEDs during pregnancy. AED-exposed infants were more frequently found to be pre-term (OR, 1.3; 95% CI, 1.1–1.6), and to have birth weight <2.500 g (OR, 1.7; 95% CI, 1.4–2.3), head circumference <2.5 percentile (OR, 2.0; 95% CI, 1.4–2.7), and low Apgar scores (OR, 1.6; 95% CI, 1.1–2.3) compared to WWoE. Small for gestational age (SGA) infants (<10 percentile) were more often born to WWE in both AED-exposed (OR, 1.2; 95% CI, 1.0–1.5) and unexposed (OR, 1.2; 95% CI, 1.0–1.4) groups. Increased MCMs were only found after in utero exposure to VPA (5.6%; OR, 2.3; 95% CI, 1.3–4.2) and AED polytherapy including VPA (6.1%; OR, 2.5; 95% CI, 1.2–5.1). Cesarean sections were performed more frequently in pregnant WWE regardless of their AED-exposure.

A group assembled by the AAN and the AES reviewed the evidence associated with the care of WWE during pregnancy which included adverse perinatal outcomes [67]. They reported on a prospective community-based study from Finland which found that WWE on AEDs during pregnancy (n = 127) are twice as likely to have SGA infants compared to WWoE (n = 24,778) (OR, 2.16; 95% CI, 1.34–3.47; absolute risk 17.3%) [68]. There was no difference in the rate of SGA in WWE not taking AEDs compared to controls. One-minute Apgar scores of less than 7 occurred more frequently in WWE taking AEDs (n = 127) compared to controls (OR, 2.29; 95% CI, 1.29–4.05) [68]. This outcome did not occur more frequently in the neonates of WWE not taking AEDs.

Seizure control during pregnancy

No population-based studies have examined seizure control during pregnancy. However some of the pregnancy registries have studied this in selected WWE. EURAP (an International Registry of AEDs and Pregnancy) reported prospectively documented seizure control and treatment in 1,956 pregnancies of 1,882 WWE [69]. Fifty-eight percent of all pregnant WWE were seizure-free throughout pregnancy. LRE (OR, 2.5; 95% CI, 1.7–3.9), polytherapy (OR, 9.0; 95% CI, 5.6–14.8), and OXC monotherapy (for tonic-clonic seizures only) (OR, 5.4; 95% CI, 1.6–17.1) predicted the occurrence of seizures. Seizure control

stayed constant during pregnancy in 63.6% of WWE pregnancies. Of those, 92.7% remained seizure-free during the complete pregnancy. There was an increase in the frequency of seizures in 17.3% of pregnant WWE and 15.9% of pregnant WWE had a decrease. The same AED treatment continued in 62.7% of the pregnancies.

The likelihood of seizing during pregnancy has been reported to be significantly decreased if there have been no seizures for a year before pregnancy according to an Australian registry-based study of 841 AED-treated pregnancies [70]. Of all AED-treated WWE, 49.7% had seizures while pregnant. The risk of having seizures during pregnancy was 24.9% with a minimum of 1 year seizure freedom before pregnancy, 22.8% with a minimum of 2 years of seizure freedom, 20.5% with a minimum of 3 years of seizure freedom and 20% with 4 years or greater of seizure freedom. The association between the length of time of seizure freedom prior to becoming pregnant and the chances of being seizure-free during and after pregnancy was the most relevant finding of this study. With 1 year of seizure freedom before pregnancy, the likelihood of seizures in pregnancy was decreased by 50–70% [70]. This is discussed further in Chapter 13.

Postpartum monitoring

Lactation

Population-based studies of breastfeeding WWE have yet to be conducted. However, pregnant WWE who were taking a single AED (CBZ, LTG, PHT, and VPA) were enrolled between 1999 and 2004 in an observational, prospective study from epilepsy centers in the USA and the UK. The implications of breastfeeding during AED therapy on cognitive outcomes in 3-year-old children were investigated in this study [71]. Of the 199 children studied, 42% were breastfed. There were no differences in IQs for breastfed children compared to non-breastfed children for all AEDs combined and for each of the four individual AED groups. Mean-adjusted IQ scores (95% CIs), across all AEDs, for children who were breastfed was 99 (96–103) while non-breastfed was 98 (95–101). This investigation does not show adverse effects of breastfeeding during AED therapy on cognitive outcomes in children exposed in utero to four common AEDs. Implications of AED use in the breastfed neonate are discussed in Chapter 18.

Epilepsy in menopause

Menopause, hormone replacement therapy

Treatment of epilepsy may disrupt the effects of hormone replacement therapy (HRT) and conversely HRT may influence the occurrence of seizures. During menopause, catamenial seizures may increase in frequency due to hyperestrogenism and then decrease afterwards. Sexual dysfunction may be exacerbated due to the lack of estrogen in menopause and epilepsy itself [72, 73]. Menopause tends to occur about 3 years earlier with a history of one or more seizures per month for much of the duration of epilepsy and lifetime use of multiple enzyme-inducing AEDs [74]. Premature ovarian failure (POF) in WWE has been noted in some studies but no predisposing factors such as epilepsy duration, seizure severity, or use of enzyme-inducing AEDs have been identified [42, 75]. As of yet, no population-based studies of menopause in WWE have been conducted. Menopause in WWE is further discussed in Chapter 21.

Bone health

Osteoporosis is associated with both menopause and the use of AEDs. The occurrence of menopause and the use of AEDs in WWE concurrently may combine to exacerbate this risk. Osteoporosis and fractures may increase in menopausal WWE because of hypoestrogenism in menopause and the use of cytochrome P450-inducing AEDs [72].

A Danish, population-based case-control study investigated fracture risk associated with various AEDs (124,655 fracture cases and 373,962 controls) using the National Hospital Discharge Register and the National Pharmacological Database [76]. After adjustment, a significant association was found between CBZ (OR, 1.18; 95% CI, 1.10–1.26), OXC (OR, 1.14; 95% CI 1.03–1.26), clonazepam (CLZ) (OR, 1.27; 95% CI 1.15–1.41), PB (OR, 1.79; 95% CI, 1.64–1.95), and VPA (OR, 1.15; 95% CI, 1.05–1.26) and the likelihood of fracture. This association was not seen in ethosuximide (ETX), LTG, PHT, primidone (PR), tiagabine (TGB), TPM, and vigabatrin (VGB). Age and gender did not affect the risk of fracture [76].

A Canadian, retrospective, cohort study of 15,792 patients with nontraumatic fractures matched with up to 3 controls (n = 47,289) investigated the relationship between AED use and nontraumatic fractures in those aged 50 years and older [77]. Pharmacy data determined current and prior AED usage. Fracture risk was significantly higher for most of the AEDs being investigated (CBZ, CLZ, GBP, PB, and PHT). The likelihood of developing a fracture ranged from an adjusted OR of 1.2 (95% CI, 1.1–1.5) for CLZ to 1.9 (95% CI, 1.6–2.3) for PHT. VPA was the only AED not associated with a greater fracture risk (adjusted OR, 1.1; 95% CI, 0.7–1.7), which persisted after adjusting for sociodemographic variables, comorbidities, and use of home care services. The risk however was not stratified by sex as both the AED exposed group and the control groups were matched for age and sex.

WWE of reproductive age are also at risk of experiencing bone loss while on AED, as shown in a prospective American study of WWE in taking AED monotherapy (CBZ, LTG, PHT, or VPA) [78]. Of note, no control group of WWoE was included for comparison. In the PHT group, a significant decrease (2.6%) was found at the femoral neck over 1 year unlike those treated with CBZ, LTG, and VPA, who did not have evidence of bone turnover or decreased bone mineral density.

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