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REVIEW ARTICLE

Sex steroid hormones and epilepsy: Effects of hormonal replacement therapy on seizure frequency of postmenopausal women with epilepsy—A systematic review

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Abstract

Background and purpose: Hormonal replacement therapy (HRT) is used for symptomatic treatment of menopause. Some evidence suggests a proconvulsant effect of estrogen and an anticonvulsant role of progesterone. Thus, the use of exogenous sex steroid hormones might influence the course of epilepsy in peri- and postmenopausal women with epilepsy (WWE). We conducted a systematic review on the impact of HRT on the frequency of seizures of WWE.

Methods: PubMed and Scopus were searched for articles published from inception until August 2022. Abstracts from the past 5 years from the European Academy of Neurology and European Epilepsy Congresses were also reviewed. Article reference lists were screened, and relevant articles were retrieved for consultation. Interventional and observational studies on WWE and animal models of estrogen deficiency were included. Critical appraisal was performed using the revised Cochrane risk-of-bias tool for randomized trials and ROBINS-E tool.

Results: Of 497 articles screened, 13 studies were included, including three human studies. One cross-sectional study showed a decrease in seizure frequency in WWE using

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†See Appendix 1 for the Gender and Diversity Issues in Neurology Task Force of the European Academy of Neurology.

combined HRT, a case–control study showed an increase in comparison with controls, and a randomized clinical trial found a dose-dependent increase in seizure frequency in women with focal epilepsy taking combined HRT. Ten studies addressing the impact of HRT in rat models were also included, which showed conflicting results.

Conclusions: There is scarce evidence of the impact of HRT in WWE. Further studies should evaluate the harmful potential, and prospective registries are needed for monitoring this population.

KEYWORDS
epilepsy, gender medicine, hormone replacement therapy, menopause

INTRODUCTION

Epilepsy is a common neurological condition in women globally, with an estimated prevalence of 6.85 cases per 1000 women [1]. This is often a life-long disorder, with impact not only on their health and well-being but also on their education, employment, and interpersonal relationships [2].

Several factors, such as inflammation, cortisol levels, and glutamatergic activity, may influence the pathogenesis of seizures. Studies suggest that estrogens have a proconvulsant effect via excitatory glutamate receptors, whereas progesterone and its metabolites (primarily allopregnanolone) exert an inhibitory effect via postsynaptic inhibitory γ-aminobutyric acid type A (GABA-A) receptors [3]. Therefore, the management of epilepsy presents a unique challenge in women, because hormonal changes during a woman's lifespan can play a significant role in epilepsy control.

Women with epilepsy (WWE) may have seizure patterns associated with changes in estrogen and progesterone levels. In catamenial epilepsy, which affects 10%–70% of WWE, seizures tend to cluster in relation to the menstrual cycle, with a greater increase of seizure frequency during a particular phase of the cycle, often around menstruation [1]. On the one hand, the lowering progesterone levels might play a significant role [1]. Similarly, menopause is characterized by severe changes in hormonal concentration [4], mainly due to estrogen decline, accompanied by the increased risk of osteoporosis, stroke, and coronary heart disease [5].

Hormonal replacement therapy (HRT), either combined (estrogen and progesterone) or estrogen alone, is often used to ease the vasomotor symptoms and other symptoms of menopause related to estrogen deficiency [6].

Considering the proconvulsant effect of estrogen, there might be an increase of seizure frequency in WWE taking combined HRT versus progesterone or estrogen-only HRT compared to WWE not taking any HRT. However, there is scarce literature on the impact of hormonal changes seen in menopause or of HRT on seizure frequency in peri- and postmenopausal WWE.

Our aim is to review, appraise, and summarize the existing literature regarding the impact of the use of HRT on the seizure frequency in menopausal WWE. To better understand the underlying physiological mechanisms, we also reviewed animal studies addressing exogenous hormonal replacement in animal models that mimic menopause.

METHODS

The systematic review protocol was developed using guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [7].

Protocol for the systematic review was submitted to PROSPERO on 9 January 2021 (registration number CRD42022302599).

The literature search was run from inception until August 2022. No language restrictions were applied. Two independent researchers (V.C. and I.C.) performed a systematic search of PubMed and Scopus databases, to identify relevant studies. We performed a systematic search using Medical Subject Headings (MeSH) and non-MeSH queries: ("hormonal replacement therapy" AND "epilepsy"); ("menopause" AND "epilepsy"); ("oestrogen replacement therapy" AND "epilepsy"); ("perimenopause" AND "epilepsy") ("postmenopause" AND "epilepsy"); ("estrogen replacement therapy" AND "epilepsy" AND "animals"). We reviewed articles from inception until 1 August 2022. Abstracts presented at the European Academy of Neurology and European Epilepsy Congress from the past 5 years were also reviewed for relevant publications. The same authors (V.C. and I.C.) then examined the reference lists identified by the search strategy, and papers of interest were retrieved for examination and included if the inclusion criteria were met.

Inclusion criteria

Types of studies

Randomized clinical trials (RCTs), nonrandomized clinical trials, case–control studies, cohort studies, and cross-sectional studies were included.

Because a priori few studies on the topic were expected, the search included experimental preclinical studies with animal models.

Participants

Patients of female sex, older than 18 years, with a previous diagnosis of epilepsy, and experiencing menopause were included.

In preclinical studies, any animal model testing the effect of HRT in surgically induced menopaused models was included.

Interventions

Any studies investigating the effect of combined/estrogen-only/progestative-only HRT on seizure frequency in women with epilepsy and menopausal/perimenopausal status were considered.

Exclusion criteria

Reviews, case reports, and case series were excluded. Articles investigating the pharmacokinetics of antiseizure medication, as well as articles studying the impact of menopause and not of HRT, were also excluded.

Measured outcomes

Seizure frequency was considered as the main outcome. Secondary outcomes were the improvement of menopause-related symptoms, treatment-related adverse effects, and measures of quality of life.

Most of the preclinical studies included were performed on seizures induced acutely; therefore, susceptibility to seizures/status epilepticus (SE)/kindle, their latencies, and total induced seizures were the main outcomes measured.

Data collection and analysis

Data were extracted independently by I.C. and V.C., using predefined forms. Disagreements were solved by consensus-based discussion.

Assessment of the risk of bias

A critical appraisal of the quality of the randomized studies was performed using the revised Cochrane risk-of-bias tool for randomized trials (ROB2) [8], and the ROBINS-E tool for observational studies [9].

Statistical analysis

Odds ratio and 95% confidence interval were the measures of associations between exposure and dichotomous outcomes. Because we were not able to conduct a meta-analysis, results were synthesized descriptively.

RESULTS

Four hundred ninety-seven articles were found. We excluded 415 articles through the initial title screen. Further details of the study selection process are documented using the PRISMA flow diagram (Figure 1). Thirteen studies were included, 10 studies on animal models and three studies on WWE.

Animal models

We first focused on studies that used animal models of estrogen removal (ovariectomized) to study the effect of estrogen and the effect of hormonal replacement on experimentally induced seizures.

Ten preclinical studies were found exploring the effects of sex hormones on epileptiform activity in estrogen-deficit states (ovariectomized) rats. Further details can be found in Table 1.

In several animal studies, estradiol was associated with observed lower seizure threshold. In one study [10], ovariectomized adult female rats receiving estrogen replacement needed fewer amygdala stimulation trials to develop the kindled state and showed greater convulsive severity after pentylenetetrazol (PTZ) injections than controls. This similar effect of estrogens has been observed in another kindling model, the anterior neocortex kindling, in adult female ovariectomized rats [11]. In this study, rats implanted with the estradiol capsule needed fewer stimulation sessions to kindle than control rats, and presented earlier onset of partial limbic seizures and of cortical generalized seizures compared to rats not receiving estradiol replacement [11]. Ovariectomized adult female rats, receiving a single oral administration of estrogen (1, 2, or 5 mg/kg) 1 h before the test, presented a reduced latent period to caffeine-induced seizures in a dose-dependent manner compared to control rats or rats treated with progesterone [12]. In line with these studies, Woolley [13] demonstrated that estradiol replacement in ovariectomized adult female rats was associated with earlier onset of seizures after kainic acid (KA) injection. Interestingly, in the same study, the authors did not report any estradiol effect on the flurothyl model of forebrain seizures [13].

The association of estradiol administration with a lower seizure threshold has not been consistently observed. Schwartz-Giblin et al. found that in ovariectomized adult female rats, treatment with 100% estradiol, administered 10–19 days before the test, was associated with no seizures after intraperitoneal injections of 1 mg/kg of picrotoxin (PTX), whereas 75% of non-treated group showed a single seizure. This effect appeared to be dose-dependent, as 10% estradiol was less effective in preventing PTX-induced seizures. This observed estradiol effect was not confirmed with seizures induced by 2 mg/kg of PTX [14]. Similarly, in another set of studies, estradiol was administered with daily subcutaneous injections, for 2 or 4 days before the test. Velísková and colleagues [15] showed that in young adult ovariectomized female rats, two subcutaneous daily injections of estradiol (2 μg/0.1 mL of oil) delayed the onset of the first KA-induced seizure and reduced

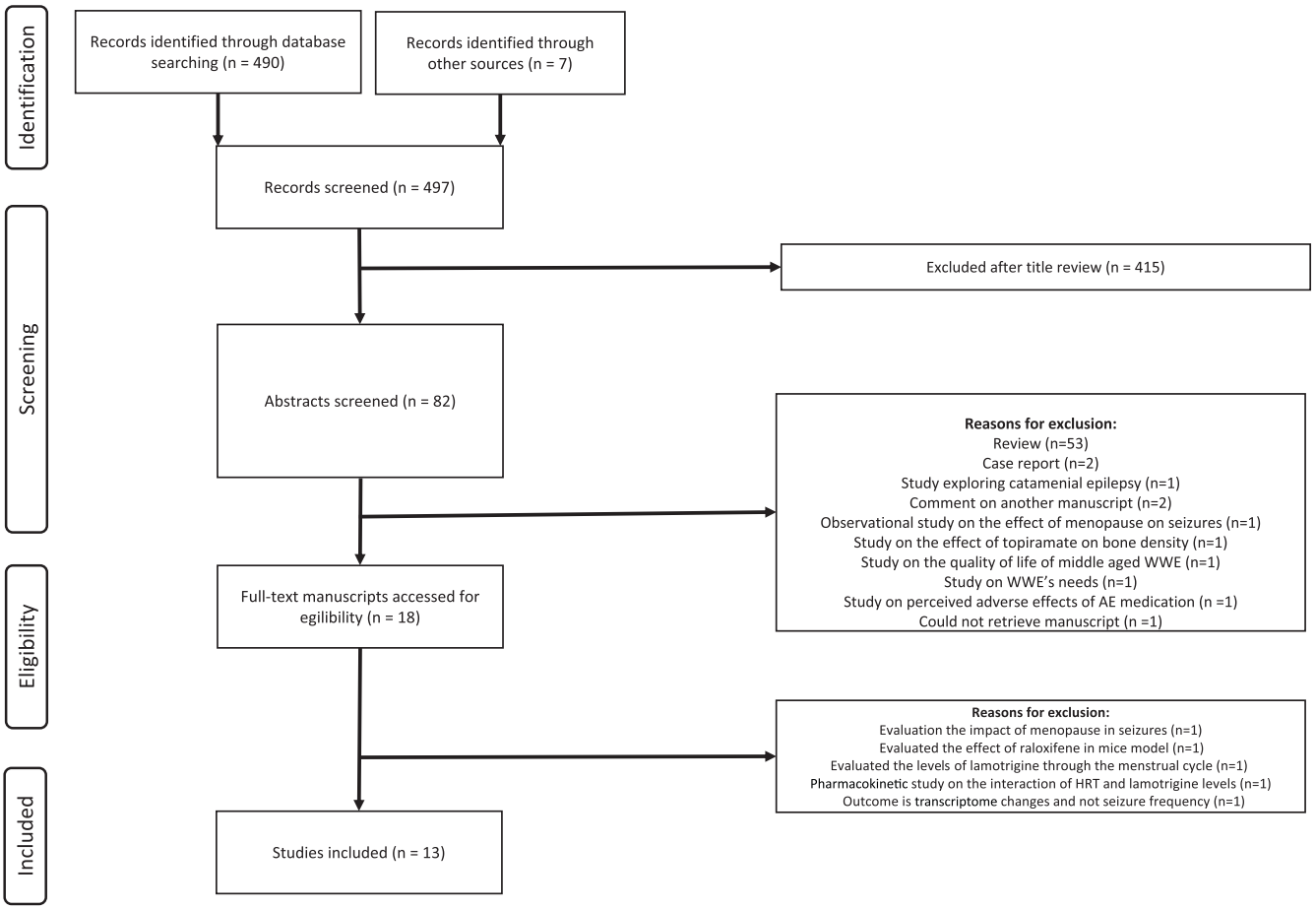

FIGURE 1 Flowchart of search criteria and article eligibility. AE, antiepileptic medication; HRT, hormonal replacement therapy; WWE, women with epilepsy.

acute mortality, without changing SE onset or preventing development of SE. In another study, estradiol injected for 4 days until the day of the test reduced the number of N-methyl-D-aspartate-induced seizures in adult female ovariectomized rats but not in male rats compared to intact females or males not receiving estrogens [16]. In a pilocarpine-induced temporal epilepsy model, the daily administration of conjugated equine estrogens (50 μg/day) was associated with decreased seizure frequency and reduced mossy fiber sprouting compared to epileptic rats not receiving the replacement therapy [17]. In a lithium–pilocarpine-induced SE model, estradiol had no effect on seizure threshold in ovariectomized female rats; however, it was associated with reduced hippocampal damage at a histological level [18].

Finally, only two studies investigated the progesterone effect on acutely induced seizures. The systemic or hippocampal administration of progesterone and 3α-hydroxy-5α-pregnan-20-one 3 h before the test in adult female ovariectomized rats was associated with increased latency to first tonic–clonic seizure and reduced number of total tonic–clonic seizures induced by PTZ [19]. This anticonvulsant effect was not confirmed in the caffeine model of seizures, where a single oral dose of progesterone (1, 2, or 5 mg/kg) administered by gavage 1 h before the test did not affect the latent period to tonic–clonic seizures [12].

Human studies

Three studies addressed the increase of seizure frequency in postmenopausal women (Table 2). A quality appraisal of these studies was made using ROBINS-E and ROB2 (Table S3). No quantitative analysis was performed due to the studies' heterogeneity.

Regarding the quality assessment of the nonrandomized studies, both studies presented a high overall risk of bias [20, 21]. The risk of bias was mainly driven by the retrospective and observational nature of the study in Abbasi et al. [20]. Furthermore, several variables that might have influenced the result, such as type of epilepsy, type of HRT, type of medication, and years of menopause, were not considered in the study design or in the report of the results. The same was true for Harden et al. [21]. Furthermore, in this study the questionnaires were emailed to participants and there was a low response rate (25%), suggesting a possible response bias, with patients with modification in the seizure frequency more likely to reply than the ones who did not experience this change [21] (see Table S3 for detailed information). No high risk of bias was identified from any domain in the RCT [22], although there were some concerns regarding the randomization process, because the recruitment stopped before the estimated sample size was reached, which might underestimate the effect of the intervention (Table S4).

TABLE 1 Summary of data from the animal studies.

Study	Species, strain	Age, weight	Epilepsy model; seizure monitoring duration and method	Hormone used	Route and timing of administration	Intervention groups	Results	Serum levels	Effect of hormones in ovariectomized female rats
Hom and Buterbaugh (1986)	Rat, Sprague Dawley	Age not mentioned, 175–250 g	1. Amygdala kindling (twice daily amygdala stimulations 4–6 h apart until kindling); EEG was recorded 1 min prior to, during, and 2 min following each AD 2. PTZ kindling (40 mg/kg ip with 2-day interval until kindling or up to 42 days max); monitored for 30 min after injection	10% 17β-estradiol in cholesterol	Two s.c. capsules implanted in dorsal neck region (one on each side of the spine), 10 days before test	a. Ovariectomized female rats implanted with a 10% estradiol in cholesterol-capsule (OVX+E) b. Ovariectomized female rats implanted with a control cholesterol-only capsule (OVX+C)	1. In amygdala kindling model • OVX+E rats required fewer daily amygdala stimulations to develop full kindling than controls • Duration of the first AD was prolonged in OVX+E rats • Threshold for AD was not different • Total cumulative AD seconds to kindle and duration of first stage V seizure were not different • 10 days after kindling was established, suprathreshold stimulation induced stage V seizure in OVX+E and in OVX rats 2. In PTZ kindling model • The convulsive severity score of OVX+E rats was greater than of OVX+C rats • OVX+E rats required fewer PTZ injections to develop fully kindled state	E_2 serum levels: 50.5 ± 4.6 pg/mL	Proconvulsant in amygdala kindling (estrogen) Proconvulsant in PTZ kindling (estrogen)
Buterbaugh (1989)	Rat, Sprague Dawley	Age not mentioned, 225–275 g	Anterior neocortex kindling (daily cortical stimulation until kindling); EEG was recorded to monitor amygdala and cortical activity	10% 17β-estradiol in cholesterol	Single s.c. capsule implanted (dorsomedial to scapulae) 10 days before test	a. Ovariectomized female rats receiving estradiol replacement (OVX+E) b. Ovariectomized female rats with no cholesterol (OVX+C; control group) (Randomized assignment to experimental group)	• OVX+E rats needed fewer stimulation sessions to kindle than OVX+C rats • Threshold for AD was not different in OVX+E and in OVX+C rats • OVX+E rats presented earlier onset of partial limbic seizures and of cortical generalized seizures compared to OVX+C rats	Not mentioned	Proconvulsant (estrogen)

(Continues)

TABLE 1 (Continued)

Study	Species, strain	Age, weight	Epilepsy model; seizure monitoring duration and method	Hormone used	Route and timing of administration	Intervention groups	Results	Serum levels	Effect of hormones in ovariectomized female rats
Schwartz-Giblin et al. (1989)	Rat, Sprague Dawley	Age not mentioned, 225–250 g[a]	PTX-induced seizures (1 or 2 mg/kg ip); monitor for 45 min Performed at least 17 days after ovariectomy Experimenter blinded to hormonal treatment	100% estradiol 10% estradiol in cholesterol	100% estradiol or 10% estradiol in cholesterol, single s.c. capsule implanted 10–19 days before test Progesterone (4 mg/kg ip) 4–5 h before test	a. Gonadectomized female rats receiving hormone replacement (estrogen, progesterone, or testosterone) b. Gonadectomized male rats receiving hormone replacement (estrogen, progesterone, or testosterone) c. Intact male rats receiving hormone replacement (estrogen, progesterone, or testosterone) d. Ovariectomized female rats with no hormone replacement	• 100% estradiol prevented rats from seizing after injection of PTX 1 mg/kg ip, whereas 75% of control rats experienced one PTX-induced seizure; this effect disappeared at a dose of 2 mg/kg • Only 25% of rats treated with 10% estradiol showed a single seizure (not significant compared to controls) • No differences in seizure occurrence were seen between gonadectomized males and females not receiving hormones	Serum E_2 level expected (based on literature) was 75 pg/mL after 100% estradiol application and 35.7 ± 4.8 pg/mL under 10% estradiol application	Partially anticonvulsant only applying 100% estradiol on lower dose of PTX-induced seizures (estrogen) No effect on high dose of PTX-induced seizures or applying 10% estradiol
Veliskova et al. (2000)	Rat, Sprague Dawley	Age not mentioned, 150–175 g	KA-induced SE (16 mg/kg ip); monitor for 5 h SE was stopped with pentobarbital (50 mg/kg ip) 5 h after SE onset SE was induced 19 h after second hormonal injection Experimenter blinded to hormonal treatment (limited to damage score)	17β-estradiol benzoate: 2 μg/0.1 mL oil	2 or 4 s.c. daily injections, 1 week after ovariectomy	a. Ovariectomized female rats receiving four estrogen injections before SE b. Ovariectomized female rats receiving two estrogen injections before SE c. Ovariectomized female rats receiving estrogen + 4 tamoxifen injections d. Ovariectomized female rats receiving 2 estrogen injections after SE e. Ovariectomized female rats receiving peanut oil (control group)	• KA induced seizures and SE in all experimental groups • Estrogen treatment before KA administration delayed the onset of first seizure but did not change the onset of SE • Estrogen injections were associated with less mortality after KA-induced seizures when compared to control group • At histological level, pretreatment with estrogens was associated with less hippocampal damage 48 h after SE, in comparison to controls or to rats receiving only posttreatment with estrogens as well as those treated with tamoxifen before estrogens	Not mentioned	Partially anticonvulsant (estrogen) Partially neuroprotective (estrogen)

TABLE 1 (Continued)

Study	Species, strain	Age, weight	Epilepsy model; seizure monitoring duration and method	Hormone used	Route and timing of administration	Intervention groups	Results	Serum levels	Effect of hormones in ovariectomized female rats
Ganapoulou et al. (2003)	Rat, Sprague Dawley	Age not mentioned, 150–175 g	Lithium–pilocarpine-induced SE (60 mg/kg ip); monitor for 3 h SE was stopped with pentobarbital (50 mg/kg ip) 3 h after SE onset SE was induced 2 h after second hormonal injection	17β-estradiol benzoate; 2 μg/rat in 0.1 mL oil	4 s.c. daily injections, 1 week after ovariectomy	a. Ovariectomized female rats receiving 4 estrogen injections (once daily) before SE b. Ovariectomized female rats receiving 4 injections of peanut oil (once daily) before SE c. Adult male rats receiving 4 estrogen injections (once daily) before SE d. Adult male rats receiving 4 injections of peanut oil (once daily) before SE	• All rats developed seizures and SE regardless sex and hormone therapy • Estrogen pretreatment reduced the latency to first seizure in male but not in ovariectomized female rats compared to respective controls • At histological level 48 h after SE, pretreatment with estrogens was associated with reduced hippocampal damage in ovariectomized female rats, whereas increased damage was observed in male rats treated with estrogens compared to rats receiving oil peanut	Not mentioned	No effect (estrogen) Sex-specific neuroprotective (estrogen)
Woolley (2000)	Rat, Sprague Dawley	~70 days, 220–250 g	1. KA-induced seizures (15 mg/kg ip); monitor for 2 h 2. Flurothyl-induced forebrain seizures (vaporized); monitor for 2 h Both tests done 6 days after ovariectomy Experiment and analysis were done blind to treatment received	10 μg 17β-estradiol benzoate in 100 μL oil 500 μg of progesterone	Estrogen: two s.c. injections, starting 3 days after ovariectomy and until 2 days before test Progesterone: s.c. injection 5 h before test	a. Ovariectomized female rats receiving estradiol replacement (OVX + E) treated with KA b. Ovariectomized female rats treated with sesame oil (OVX + O) treated with KA c. Ovariectomized female rats receiving estradiol replacement (OVX + E) treated with flurothyl d. Ovariectomized female rats receiving sesame oil (OVX + O) treated with flurothyl e. Ovariectomized female rats receiving estradiol + progesterone replacement (OVX + EP) treated with flurothyl	1. KA-induced seizures • KA-induced seizures were similar in OVX + E and OVX + O rats • OVX + E rats show KA-induced seizures earlier than OVX + O rats 2. Flurothyl-induced forebrain seizures • No effect of estradiol or estradiol + progesterone was observed on flurothyl-induced seizures	Not mentioned	Partially proconvulsant limited to limbic seizures (estrogen)

(Continues)

TABLE 1 (Continued)

Study	Species, strain	Age, weight	Epilepsy model; seizure monitoring duration and method	Hormone used	Route and timing of administration	Intervention groups	Results	Serum levels	Effect of hormones in ovariectomized female rats
Kalkbrenner and Standley (2003)	Rat, Long–Evans	Age not mentioned, 250–300 g	NMDA-induced seizures (20 μg/μL, intraventricular injection); EEG monitor with hippocampal electrode for 20 min minimum	10 μg 17β-estradiol in 100 μL oil	Four s.c. injections; seizure test was done on 4th day of treatment	a. Ovariectomized female rats with estrogen replacement (OVX + E) b. Ovariectomized female rats (OVX) c. Nonovariectomized female rats (NOVX) d. Male rats given exogenous estrogen (M + E) e. Male rats receiving no estrogen (M)	• Estradiol treatment reduced number of seizures in OVX + E female rats compared to OVX rats and restored it to the condition typical of preovariectomy (NOVX) • Latency to first seizure and seizure duration were not different in OVX + E rats compared to OVX rats • No effect of estrogen replacement on all seizure parameters was seen in male rats compared to intact female and male rats not receiving estrogens	Not mentioned	Anticonvulsant, sex-specific (estrogen)
Borecki et al. (2010)	Rat, Wistar	Age not mentioned, 210–215 g	Caffeine-induced seizures (300 mg/kg ip)	Estrogen (1, 2 or 5 mg/kg) Progesterone (1, 2, or 5 mg/kg)	Estrogen: single oral administration (by gavage) 1 h before test Progesterone: single oral administration (by gavage) 1 h before test Hormones were administered 1 week after ovariectomy	a. Ovariectomized female rats receiving increasing dosages of estrogen b. Ovariectomized female rats receiving increasing dosages of progesterone c. Ovariectomized female rats receiving distilled water d. Ovariectomized female rats receiving tamoxifen prior to oral estrogen administration e. Intact female rats receiving hormones (FSH or LH) or distilled water	• Estrogen, but not progesterone, reduced latent period to caffeine-induced tonic–clonic seizures • Tonic–clonic convulsive seizures have been observed in all rats treated with estrogen, progesterone, and vehicle	Not mentioned	Partially proconvulsant in a dose-dependent manner (estrogen)

TABLE 1 (Continued)

Study	Species, strain	Age, weight	Epilepsy model; seizure monitoring duration and method	Hormone used	Route and timing of administration	Intervention groups	Results	Serum levels	Effect of hormones in ovariectomized female rats
Pereira et al. (2009)	Rat, Wistar-EPM1	120 days, 200 g	Pilocarpine-induced temporal lobe epilepsy (350 mg/kg); video-monitoring for 30 days after pilocarpine-induced SE; when epileptic condition was confirmed, rats were ovariectomized	Conjugated equine estrogens (50 μg/day)	Daily oral administration (by gavage) for 30 consecutive days, starting 4 days after ovariectomy	a. Intact female epileptic rats (GPC) b. Ovariectomized female rats (GOC) c. Intact female rats (GNC) d. Ovariectomized epileptic female rats treated with estrogen (GPE) e. Ovariectomized epileptic female rats that received propylene glycol vehicle (GPV)	• Ovariectomized rats that received estrogen (GPE) presented a reduction in number of chronic epileptic seizures compared to ovariectomized epileptic rats receiving vehicle (GPV) • Mossy fiber sprouting was more pronounced in ovariectomized epileptic rats not receiving estrogen than in epileptic ovariectomized rats treated with estrogen replacement • Histological analysis showed that rats that received estrogens presented neuronal loss in the CA3 layer, whereas those that received propylene glycol, besides changes in the hippocampal structure and loss in CA3, also showed neuronal loss in CA1 and dentate gyrus	Not mentioned	Neuroprotective and antiepileptic (estrogen)
Rhodes and Frye (2004)	Rat, Long–Evans	55 days, weight not mentioned	PTZ-induced seizures (70 mg/kg); monitor for 10 min; 1 week after ovariectomy	Progesterone (500 μg in oil) 3α,5α-THP (500 μg in oil)	Progesterone: s.c. or intracerebral injection in dorsal hippocampus, 3 h before testing 3α,5α-THP: s.c. injection 3 h before testing	a. Ovariectomized female rats receiving progesterone replacement b. Ovariectomized female rats receiving 3α,5α-THP c. Ovariectomized female rats receiving sesame oil (control)	• Systemic and hippocampal administration of progesterone and 3α,5α-THP increased latency to first tonic–clonic seizure and reduced number of total tonic–clonic seizures	Not mentioned	Anticonvulsant (progesterone)

Abbreviations: 3α,5α-THP, 3α-hydroxy-5α-pregnan-20-one; AD, afterdischarge; E_2, estradiol; EEG, electroencephalography; FSH, follicle-stimulating hormone; GNC, intact female rats; GOC, ovariectomized female rats; GPC, intact female epileptic rats; GPE, ovariectomized epileptic female rats treated with estrogen; GPV, ovariectomized epileptic female rats that received propylene glycol vehicle; KA, kainic acid; LH, luteinizing hormone; M, male rats receiving no estrogen; M + E, male rats given exogenous estrogen; max, maximum; NMDA, N-methyl-D-aspartate; NOVX, nonovariectomized; OVX, ovariectomized; OVX + C, ovariectomized rats receiving control; OVX + E, ovariectomized rats receiving estrogen replacement; OVX + EP, ovariectomized rats receiving estrogen + progesterone replacement; OVX + O, ovariectomized female rats treated with oil; PTX, picrotoxin; PTZ, pentylenetetrazole; s.c., subcutaneous; SE, status epilepticus.

[a]All female and half of male rats arrived gonadectomized from the vendor.

TABLE 2 Summary of data from the studies selected from qualitative analysis.

Study	Type of study	Intervention/ exposure	Control group	Mean age, years (range)	Number of participants	Type of HRT	Number of antiepileptic medications	Type of seizures/ epilepsy	Results
Abbasi et al. (1999)	Cross-sectional	Hormonal replacement therapy	-	Premenopausal: 33.3 Perimenopausal: 44.7 Postmenopausal: 53.4	107 WWE • 46 menopausal • 15 perimenopausal 46 premenopausal	Menopausal women: • 40% estrogen only • 60% combined	Not specified	Premenopausal: • 57% generalized • 79% focal Perimenopausal: • 60% generalized • 73% focal Postmenopausal: • 52% generalized • 78% focal	71% no change in seizure frequency 16% improved 13% worsened
Harden et al. (2000)	Case–control	Hormonal replacement therapy	Menopausal/ perimenopausal WWE without HRT	Menopausal: • HRT group: 54 (41–58) • Controls: 53 (40–86) • Perimenopausal: 46 (38–55)	81 WWE • 42 menopausal • 39 perimenopausal	Menopausal WWE, 38% taking HRT • 31% estrogen only • 63% combined • 6% unknown Perimenopausal WWE, 20% taking HRT (type of HRT not reported)	Menopausal WWE: median = 2 (range = 0–2)	Menopausal: • 86% focal epilepsy • 14% generalized epilepsy Perimenopausal: • 92% focal epilepsy • 8% generalized epilepsy	62.5% of menopausal WWE taking HRT reported worsening vs. 11.6% of controls • Combined HRT 50% (OR = 7.67, 95% CI = 1.36–43.13) • Estrogen-only 80% (OR = 30.67, 95% CI = 2.52–373.55). In perimenopausal women, HRT was not associated with increase in seizures

TABLE 2 (Continued)

Study	Type of study	Intervention/ exposure	Control group	Mean age, years (range)	Number of participants	Type of HRT	Number of antiepileptic medications	Type of seizures/ epilepsy	Results
Harden et al. (2006)	RCT	Hormonal replacement therapy	Placebo	53 (45–62)	21 menopausal WWE • 6 placebo • 8 single dose • 7 double dose	Combined HRT (0.625 mg of conjugated equine estrogens + 2.5 mg of medroxyprogesterone acetate) single or double dose	Median = 1 (range = 0–3)	Focal epilepsy	Placebo: no increase in the frequency of seizures Single dose: 37.5% patients had increase in the frequency of seizures (OR = 8.27, 95% CI = 0.35–297.61) Double dose: 42.9% had increase in the frequency of seizures (OR = 10.11, 95% CI = 0.41–247.48)

Abbreviations: CI, confidence interval; HRT, hormonal replacement treatment; OR, odds ratio; RCT, randomized clinical trial; WWE: women with epilepsy.

In the cross-sectional study on the effect of menopause on WWE [20] (Table 2), seizure frequency in pre-, peri-, and menopausal women, as well as the temporal pattern of seizures with the onset of menopause, were compared. Perimenopausal women, compared to premenopausal and menopausal, had fewer seizures, but there was no difference in seizure intensity. However, these findings were not adjusted for other factors, such as seizure type or type/number of antiepileptic medication (AEM) used. Of the 49 participants who had epilepsy before menopause, 41% described a worsening in their seizure frequency, 27% improvement, and 33% no definitive change. Thirty-one (51%) of the 61 menopausal participants had used HRT, and of those, 22 (71%) did not notice any change in the seizure pattern, five (16%) described improvement, and four (13%) noticed worsening [20]. Regarding the type of HRT prescribed, only 15 women could correctly identify the type of HRT they were taking. Of those, six were taking combined HRT and nine were taking estrogen without progesterone. In the former group, three (50%) reported a decrease in seizure frequency and the other half no change. Of those taking estrogen-only HRT, one described an increase and eight reported no change in their seizure frequency.

In the case–control study on the impact of menopause and HRT in perimenopausal and menopausal women [21], data from 42 menopausal women were analyzed; 28% reported no change in seizures with menopause, 41% a decrease, and 31% an increase [21]. Sixteen of the 42 WWE were taking HRT. The types of HRT were variable, but most WWE (69%) were taking both estrogen and progesterone or combined formulations. Of the HRT group, 62.5% ($n=10$) reported an increase in seizures, compared to three (11.5%) of 26 who were not taking HRT. However, if analyzed taking the type of HRT into consideration, 50% of the 10 patients taking combined HRT reported worsening versus 80% of the five patients taking estrogen-only formulations. The subgroup of women with catamenial epilepsy pattern ($n=16$) most often reported improvement of seizures with menopause, and the use of HRT worsened seizure frequency in this group.

In the perimenopausal group, data from 39 patients were analyzed; 23% reported no change in seizure frequency, 64% an increase, and 12% a decrease. Eight of these women were taking HRT, and there was no clear effect of this treatment on seizure exacerbation. However, the authors found an increase in seizure frequency in patients with catamenial epilepsy in this group [21].

Subsequently, the same authors performed an RCT addressing the effect of HRT on seizure frequency of WWE [22]. This RCT enrolled 21 patients with focal epilepsy (which did not reach the estimated sample size minimum of 40 patients for each arm), who were randomized to a single dose of combined HRT (consisting of 0.625 mg of conjugated equine estrogens + 2.5 mg of medroxyprogesterone acetate) or double dose of combined HRT. Five of the seven patients who were randomized to the double dose discontinued the trial; one was lost to follow-up, one discontinued due to the increase in the number of seizures, and three discontinued due to HRT-related adverse effects. In the single-dose group, one patient discontinued the treatment due to HRT-related adverse effects. This study found an association between increased seizure frequency and seizure severity with increasing HRT dose. There was little change in the AEM. In two patients taking lamotrigine (LTG) who were randomized to the HRT group (single dose), LTG levels in serum decreased by 25%–30%, with one of them (medicated solely with LTG) having an increase in seizures during treatment [22].

None of the studies included collected data on the improvement of menopause-related symptoms or quality of life.

DISCUSSION

Our review shows that there is scarce and contradictory preclinical and clinical literature on the effects of HRT in female animals and WWE and its impact on seizure control [17, 23].

The preclinical data in animal models have shown variable results. Rodents have been considered appropriate models for the study of human menopause. However, it is noteworthy that there are some important differences between human and rodent reproductive senescence, as rodents have an estrous cycle rather than a menstrual cycle and potentially mature ovulatory follicles also in older age [23]. Furthermore, rodents during their reproductive senescence show high levels of 17β-estradiol and moderate levels of progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), whereas human menopause is characterized by low values of 17β-estradiol and increased levels of FSH and LH [23]. Although different rat models are currently used to study human menopause [23], all studies included in this review used the ovariectomized model, which has been considered the gold standard for the study of gonadal hormone effects in female rodents [23].

Estrogen replacement in ovariectomized rats was investigated on several models of seizure, SE, and kindling, and it has been associated with both proconvulsant [10–13] and anticonvulsant [14–17] effect, whereas one study reported no effect [18].

The antiepileptic effect was investigated and reported only in the study by Pereira et al. [17]. The results shown in these studies suggest that (i) estradiol effect is seizure type-specific and (ii) estradiol facilitates the development of secondarily generalized seizures.

The contradictory results observed in the acute preclinical studies may be due to different factors. The first critical factor is the model used to induce seizures, SE or kindling; each model is characterized by different ictogenic mechanisms, and estrogens may affect them differently. Secondarily, estrogens doses, routes of administration, pharmaceutical plans, and chemical forms may lead to different serum levels of this hormone; however, only two studies measured and reported it [10, 14]. Ultimately, the method of seizure detection may affect the accuracy of the results, as visual observational studies may miss nonconvulsive and nonmotor seizures, whereas studies performing electroencephalography (EEG) are able to provide more precise data on seizure frequency and a full detailed analysis of the

epileptiform activity recorded; only three of the studies included in this review performed EEG regularly [10].

Only one study [17] explored HRT in epileptic seizures and not in evoked seizures or SE. The authors explored the effect of HRT in a model of temporal lobe epilepsy. In this study, only epileptic female rats were ovariectomized and then treated with estrogens, mimicking more closely the human condition. The authors showed a reduction in the number of chronic epileptic seizures and in mossy fiber sprouting as well as limited damaged areas [17]. The neuroprotective result observed in epileptic female rats treated with estrogens [17] is in line with the neuroprotective effect reported in two studies in which histological analysis was performed 48 h after SE [15, 18]. However, seizures were video-recorded and not EEG-detected, and therefore nonmotor seizures might have been missed, which limits the validity of the results.

Further discussion of the results of the preclinical results can be found in Appendix S1.

Regarding human studies, the available clinical data we reviewed here present significant limitations. Due to the low number of studies and participants included, as well as the design of the study, only limited conclusions can be made. The two nonrandomized studies were cross-sectional, and therefore a temporal relation could not be evaluated, with the results prone to recall bias from the participants. The two studies used self-reported questionnaires to access seizure frequency, and whereas Abbasi et al. [20] used the Chalfont severity scale [24] to assess seizure severity, the method to measure severity in the work written by Harden et al. [21] is not clear (Table 1). This can also contribute to recall bias and heterogeneity in the measurement of the outcomes. Furthermore, several variables that might have influenced the course of epilepsy, such as type of epilepsy or number of drugs, were not considered in the analysis of the results. The only available RCT was started before the results of the Women's Health Initiative study results were published. The latter was designed to evaluate the risks and benefits of HRT in healthy postmenopausal women aged 50–79 years. The study showed an increased risk of thromboembolic events in the combined HRT arm [25]. The subsequent RCT by Harden et al. [22] did not reach the expected sample size, and it might therefore underestimate the effects of combined HRT on seizure frequency. Furthermore, this study only explored the effect in focal epilepsy, which might not be extrapolated to generalized forms of epilepsy, and the follow-up length was only 84 days.

The quality of the evidence on estrogen-only or progesterone-only formulation is even lower, as it is only reported in cross-sectional studies.

Furthermore, findings on menopausal women, who have low levels of sex hormones, might not apply to perimenopausal women, who usually present with a higher and unpredictable estrogen/progesterone ratio [21]. Harden et al. assessed the influence of HRT in this population and found no impact [21]. However, as previously stated, the study has several limitations, and the type of HRT was not specified in the article.

One should also take into consideration that the three included studies were performed in the 1990s and early 2000s, and at that time most patients were treated with AEM such as phenytoin, phenobarbital, valproate, and primidone, which have far more interactions than most drugs currently used in the treatment of WWE.

We did not explore the effect of menopause itself on seizures. However, this was addressed by Harden et al. [21] and Abbasi et al. [20]. Whereas Abbasi et al. noticed an increase in seizure frequency after menopause in 41% of WWE, the opposite was noticed in the study by Harden et al., describing a decrease in seizure frequency in 41%, in women with catamenial epilepsy. Another study on 27 WWE found that 27% ($n=7$) noticed worsening after menopause, whereas the remaining 73% ($n=20$) did not notice any change in seizure pattern [26]. However, these three studies were retrospective and hence prone to recall bias.

Of note, in the study by Harden et al. [22], one of the patients with increased seizures was taking LTG as monotherapy treatment. LTG is a commonly used drug in both focal and generalized epilepsies. Postmenopausal women seem to have a higher clearance of LTG than younger women with regular menstrual cycles [27]. Furthermore, HRT decreases the levels of LTG, which might further contribute to an increase in seizure frequency [28].

Despite the limitations, the three studies, taken together, suggest an increase in the frequency of seizures in menopausal WWE taking HRT, both with combined and with single estrogen formulations. This in line with most of the studies on rat models; however, the findings of the preclinical studies should be interpreted with caution, as they do not include animals pretreated with antiepileptic drugs; thus, it cannot be excluded that potential pharmacokinetic interactions between hormones and antiepileptic drugs may result in differences of the levels of circulating sex hormones between humans and animals.

Furthermore, other potential adverse effects of HRT, such as the increase in cardiovascular risk, must be weighed against the benefits of HRT in the treatment of sudomotor symptoms, bone mass, and improvement of quality of life [29]. For instance, WWE taking phenytoin, carbamazepine, and valproic acid have lower calcium serum concentrations than WWE taking LTG. Furthermore, phenytoin is associated with an increase in bone-specific alkaline phosphatase, an enzyme related to bone turnover [30]. Therefore, some adverse events are also associated with increased bone turnover and hence these patients might further benefit from the effect of HRT on bone mass.

Finally, peri- and menopausal cis WWE are not the only at-risk group. Transgender male-to-female women with epilepsy are treated with gender-affirming hormones with different dosages and for longer periods [31]. Future research should expand the knowledge of the impact of exogenous hormonal treatment and address this issue in this increasing and often neglected demographic group.

Our review, albeit systematic, is not without limitations. The scarce literature and the positive results in the nonrandomized studies might be due to publication bias, and studies with negative results might not get to publication. To minimize this, we also reviewed abstracts from two international general neurology and epilepsy congresses. Furthermore, summarizing the existing data through

meta-analysis was not possible due to different study designs and heterogeneity across studies.

The impact of hormones during epilepsy has been a matter of discussion for clinicians and researchers [32]. Estrogen inhibits GABA transmission and potentiates glutamatergic transmission, whereas progesterone metabolites are barbiturate-like modulators of GABA receptors and suppress epileptiform discharges [33, 34]. As sex hormones fluctuate during the menstrual cycle, this might lead to seizure clusters. During menstruation and ovulation, the ratio estrogen/progesterone is higher, and hence favors a proconvulsive state [32]. One of the best examples of this interaction is catamenial epilepsy [33]. Herzog and colleagues proposed three patterns of seizure exacerbation with menstruation: perimenstrual and periovulatory in normal cycles and luteal in inadequate luteal phase cycles, which refers to low secretion of progesterone during the second half of the cycle, regardless of the occurrence of ovulation [33]. This sensibility to hormonal variations seems to accompany these women through their lifetime and pose new challenges during reproductive and nonreproductive stages of these women's lives; during pregnancy, they often experience better seizure control compared to women with noncatamenial epilepsy, possibly due to the absence of cyclical hormone variations and increase in progesterone levels [35]. In line with this, in our review, the subgroup analysis in the work written by Harden and coauthors [21] showed that these patients more often reported improvement of seizures during menopause and worsening of seizure frequency following HRT [21].

Several gaps in knowledge still exist regarding this key issue in WWE's health. As another RCT would raise safety and ethical concerns, prospective monitoring registries might be a solution to understand the "real world" impact of HRT in WWE. Prospective studies would also minimize recall bias and would provide better data to answer this question, which might ultimately have an impact in the treatment and quality of life of WWE. Several examples of prospective registries exist in the field of women's issues in epilepsy. Most notably, in epilepsy, EURAP is an observational registry of researchers from several countries, established in 1999, which aimed to monitor the effect of epilepsy and AEM in WWE during pregnancy [36]. These registries could serve as an example for a prospective multicentric observational study of WWE of nonchildbearing age, which should ideally include variables such as type of epilepsy (including catamenial epilepsy), etiology, gender at birth, age at first seizure, age at menarche and menopause, AEM used, type of HRT used and dosage, concomitant medication, seizure control, and seizure frequency, as well as comorbidities (such, as for instance, cerebrovascular disease). This same model could be used to address hormonal therapy in noncisgender women, including gender-affirming therapies among transgender populations.

This review highlights the lack of high-quality evidence on the impact of HRT in cisgender WWE. Due to the low number of studies and participants included, as well as the design of the study, the conclusions we can draw from it are limited.

In conclusion, the potential risk of increased seizure frequency with HRT in WWE remains to be assessed with high-quality studies. In general, the risk must be weighed against its potential benefits, possibly with more frequent follow-ups by their treating physician following HRT introduction.

CONFLICT OF INTEREST STATEMENT

V.C. has received speaking fees from Bial, unrelated to this project. E.M. has received honoraria from Medtronic and The Element for consulting. She has received a research grant from France Parkinson. M.T.F. is the Chief Scientific Officer and cofounder of the Women's Brain Project. In the past 2 years, she has received consulting and speaking fees from Roche, Eli Lilly, and Lundbeck unrelated to this project. G.C. has received consulting fees from PassageBio unrelated to this project. E.R.L. is a full Professor of Neurology at the Ural State Medical University, of which education is the primary function, and is not employed by the Russian government. The remaining authors do not have any affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 1

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