Heliyon 9 (2023) e20098

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Differential effects of carbamazepine and levetiracetam monotherapy on reproductive endocrine function in Nigerian women with epilepsy

Luqman Ogunjimi [a,*], Yaria Joseph [c], Alabi Akinyinka [a], Aderinola Aderonke [a], Osalusi Bamidele [b], Falujo Bolanle [a], Murtala Abdullahi [a], Dada Olaide [a], Oyebowale Mariam [a], Oyenuga Ibironke [a], Fatai Fehintola [d], Ogunniyi Adesola [c]

[a] Department of Pharmacology and Therapeutics, Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University, Remo Campus, Sagamu Ogun State, Nigeria
[b] Department of Medicine, Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University, Remo Campus, Sagamu Ogun State, Nigeria
[c] Department of Medicine, University College Hospital, Ibadan, Oyo State, Nigeria
[d] Department of Pharmacology and Therapeutics, University College Hospital, Ibadan, Oyo State, Nigeria

A B S T R A C T

Objective: This study is aimed at comparing differential effect of Levetiracetam (LTC) monotherapy and Carbamazepine (CZP) monotherapy in W omen with epilepsy (WWE) on gonadal hormone.
Methods: 87 WWE were recruited comprising randomly of 46 and 41 on CZP and LTC group respectively with diagnosis and classification based on International League Against Epilepsy (ILAE). Reproductive hormones (Luteinizing Hormone (LH), Follicle stimulating hormone, progesterone, estradiol and testosterone) were assayed. National Hospital Seizure Severity Scale (NHSS) and Zung self-reporting depression scale (ZSRDS) were used to assess the seizure severity and the mood respectively. Data was analyzed using Statistical Package for Social Sciences (SPSS) version 20. The Chi-square test was used to compare categorical variables while Student's t-test or its non-parametric equivalent where appropriate were used to compare continuous variables.
Results: Clinical characteristics were comparable in both groups except for ZSRDS ($p = 0.048$), NHSS ($p = 0.012$) and hip circumference ($p = 0.037$). The CZP group had a higher ASEX score and proportion of WWE with clinically significant sexual dysfunction ($p < 0.001$). WWE on LTC had similar hormonal profiles with those on CZP except for a higher median serum testosterone level ($p = 0.004$), and lower median serum LH ($p = 0.006$). Age was negatively associated with serum testosterone level for the 25th, 50th, and 75th quartile. However, the differential effect for AED type was only significant for the 25th quartile; with higher values in LTC.
Conclusion: The therapeutics implication of lower LH and testosterone levels in the LTC group compared to CZP group need to be explored.

1. Introduction

The interaction between the sex steroid hormonal axis, epilepsy, and the medications used to treat epilepsy remain complex [1]. Women with Epilepsy (WWE) frequently experience a higher prevalence of endocrine dysfunction and reproductive abnormalities including menstrual irregularities when compared to the general population [2]. Poorer sexual function in WWE has also been described [3–5] and the need to explore the complex relationship between epilepsy, Anti-Epileptic Drugs (AEDs), sex steroid hormone

* Corresponding author. Department of Pharmacology and Therapeutics, Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University, Remo Campus, Sagamu, Ogun State, Nigeria.
E-mail address: luqmanogunjimi@yahoo.com (L. Ogunjimi).

https://doi.org/10.1016/j.heliyon.2023.e20098
Received 16 November 2022; Received in revised form 21 August 2023; Accepted 12 September 2023
Available online 13 September 2023

and attending negative effect. AEDs, interictal and ictal discharges responsible for alterations in the sex steroid hormonal axis at the level of the hypothalamus and the pituitary has been proposed [6]. Thus, understanding the differential effects of AEDs and sex steroids hormones remains a critical step for effective therapies that are most likely to have impact on overall quality of life in WWE [7,8]. Several newer-generation AEDs have undergone comparative trials demonstrating efficacy equal to and tolerability at least equal to or better than older AEDs as first-line therapy.(Abou-Khalil, 2016) Levetiracetam (LTC) A newer generation AEDs which acts by binding to the synaptic vesicle protein SV2A, leading to a decrease in neurotransmitter release in a state of neuronal hyperactivation (Chakravarthi et al., 2015; Fukuyama et al., 2012), has shown excellent pharmacokinetics profile (Chakravarthi et al., 2015). LTC's favorable pharmacokinetics profile, and lower incidence of drug interactions when compared to other anticonvulsants contribute to its growing use(Chakravarthi et al., 2015; Shetty., 2013). However, there is no convincing data to show endocrine side effect of LTC during treatment as previously reported in a study on animal subject. [9]; 2009). Few studies have evaluated the differential effect of AEDs on the growing burden of reproductive endocrine dysfunction among WWE in Sub Africa [2,9–11]. Thus, the aim of this study was to compare the effect of LTC monotherapy and Carbamazepine (CZP) monotherapy in WWE on gonadal hormone and other gynecological characteristics.

2. Methods

Using clinic record as sampling frame with about 196 WWE, 70 WWE were excluded because they did not meet inclusion criteria and 87 WWE were randomly selected from the remaining 126 WWE. 87 consenting adults aged between 16 and 40 years on LTC or CZP monotherapy were randomly selected among WWE attending Neurology clinic at University College Hospital (UCH) Ibadan after obtaining ethical approval. Patients were strictly on monotherapy of either LTC [41(47%)] or CZP [46(53%)]. Diagnosis and classification of epilepsy were in accordance with recommendation by the 2017 International League against Epilepsy (ILAE) [12]. Patients with hypo-gonadism, hypopituitarism, retroviral infection, thyroid dysfunction, Cushing's disease, steroid use, use of oral or injectable contraception, previously or recently diagnosed diabetes, those on hormonal replacement therapy, previously or currently use of other AED apart from LTC/CZP, those using multiple AED and those with an ultrasound confirmed pregnancy were excluded. An interviewer-based and pre-established questionnaire was engaged in obtaining history about seizure characteristics which include age, age of onset, seizure description, last duration and etiology of epilepsy. In addition, details of obstetric and gynecologic history such as menarche, cycle length, ketamania, periods of amenorrhea, Last Menstrual Period (LMP), galactorrhoea, frequency of intercourse, libido and dyspareunia were documented. Collection, handling and analysis of the hormonal sample was as we previously described [13]. A few validated scales were used for neuropsychological assessment. National Hospital Seizure Severity Scale (NHSSS) which contains seven seizure-related factors and generates a score from 1 to 27 and Zung Self-Reporting Depression Scale (ZSRDS) was used to assess the severity and mood of the participants respectively. Arizona Sexual Experience Scale (ASEX) was used to assess the sexual interest and function which contains 6 questions which are: How strong is your sex drive, how easily are you sexually aroused, how easily does your vagina become moist, how easily can you reach orgasms and are your orgasms satisfying, with values ranging from 1 to 6 and highest score of 30. The higher the score indicating more sexual dysfunction. All previously mentioned variables were entered for non-parametric bivariate analysis to determine potential predictors to be selected for multivariate analysis. The Shapiro-Wilks test

Table 1
Socio-demographic and clinical characteristics of participants.

variables	czp N = 46	ltc N = 41	*P*-value
AGE, MEAN (SD)	30.3 (8.1)	27.9 (7.3)	0.207
aGE OF ONSET, MEAN (SD)	21.4 (13.1)	20.2 (9.9)	0.653
REGULAR MEDICATION, N (%)	41(89.2)	31(75.6)	0.096
TYPES OF EPILEPSY N (%)			
FOCAL ONSET	24 (52.2)	21 (51.2)	0.550
GENERALIZED ONSET	22 (47.8)	20 (48.8)	
ETIOLOGY, N (%)			
STRUCTURAL	33 (71.7)	19 (46.3)	0.059
METABOLIC	1 (2.2)	2 (4.9)	
IMMUNE	1 (2.2)	–	
UNKNOWN	11 (23.9)	20 (48.8)	
BMI, MEAN (SD)	24.3(4.4)	24.3(4.2)	0.996
EPILEPTIFORM PATTERN N (%)			
PRESENT	44 (97.8)	36 (87.8)	0.549
ABSENT	2 (2.2)	5 (12.2)	
LAST SEIZURE EPISODE, N (%)			
< 2 YEARS	40 (87.0)	40 (97.6)	0.348
> 2 YEARS	6 (13.0)	1 (2.4)	
NHSS-3 SCORE, MEAN (SD)	16.2 (6.5)	12.6 (6.4)	0.012*
ZSRDS, MEDIAN (IQR)	32(28–36)	28 (25.5–33)	0.048*
HIP CIRCUMFERENCE, MEAN (SD)	88.2 (12.8)	82.6 (11.9)	0.037*

CZP – Carbamazepine, LTC – Levetiracetam, SD – Standard Deviation, N – Number, IQR – Inter-Quartile Range, ZSRDS – Zung Self-Reporting Depression Scale, NHSS – National Hospital Seizure Severity, *Statistically significance, BMI – Body Mass Index.

was carried out to decide if the variables were normally distributed or not. Outcome variables of interest for this study were serum levels of various hormones. Independent variables that showed signification association with outcome of interest after univariate regression were used to create the quantile regression model. To arrive at a minimum sample size, Pocock's formula for the comparison of mean of two-groups was used. Due to the difficulty with obtaining a larger dataset and non-parametric distribution of variables, bootstrapping technique was used to select predictors for multivariate models. Quantile regression model was chosen due to the non-parametric distribution hormonal variables and their left and right skew respectively. A thousand bootstrapped samples were drawn from the imputed data set. Stata version 12 was used for data analysis. The level of statistical significance was set at p–value of <0.05.

3. Results

3.1. Clinical and socio-demographic characteristics of WWE

There was no statistical significance difference between randomly selected CZP 46(53%) and LTC 41(47%) group except for depression as measured by ZSRDS ($p = 0{,}048$), seizure severity as measured by NHSS ($p = 0.012$) and Hip circumference ($p = 0.037$). (See Table 1).

3.2. Effect on gynecological status

With regards to gynecological history, both groups had similar age of menarche, menstrual cycle length and period days; p-value: 0.094, 0.070 & 0.552 respectively. A higher number of the LTC group complained of hirsutism, 8 (19.5%), inter-menstrual bleeding, 7 (17.1%), and dyspareunia, 13 (31.7%) as opposed to 1 (2.2%) from the CZP group. However, the CZP group had a higher ASEX score and proportion of WWE with clinically significant sexual dysfunction, $p < 0.001$. (See Table 2).

3.3. Differential effect of CZP and LTC on hormone

WWE on LTC had similar hormonal profiles with those on CZP as shown in Table 3 except for a higher median serum testosterone level, p: 0.004, and lower median serum Luteinizing hormone (LH), p: 0.006.

3.4. Relationship between AED and testosterone level

The differential effect for AED type was only significant for the 25th quantile; those on LTC having higher values compared to those on CZP. As expected, age was negatively associated with serum testosterone level for the 25th, 50th, and 75th quartile. Table 4 shows regression coefficient and p-value.

4. Discussions

This study demonstrated that the sex steroid hormonal levels were comparable in both groups except for higher luteal phase LH, lower testosterone, higher ASEX score which is indicative of poorer sexual function, higher number of people with sexual dysfunction among WWE on CZP compared to those on LTC monotherapy. The general notion that hepatic enzyme– inducing AEDs, specifically cytochrome P450 3A4 (CYP3A4) inducers affect the metabolism of endogenous sex hormones and therefore contribute to the dysregulation of the hypothalamic-pituitary-ovarian axis was further demonstrated in our study with significant reduction in levels of testosterone in those on CZP, an enzyme inducing AED, compared to values of WWE on LTC, a non-hepatic enzyme inducing AED. Further analysis with quartile reduction analysis using serum testosterone level as outcome variable revealed that differential effect of

Table 2
Gynecological characteristics of participants.

	czp	ltc	*P*-value
MENARCHE, MEAN (SD)	11.5 (1.1)	11.9 (1.4)	0.094
PERIOD DAYS, MEAN (SD)	4.4 (0.9)	4.8 (0.9)	0.070
MENSTRUAL CYCLE LENGTH, MEAN (SD)	26.6 (2.2)	27.5 (3.4)	0.552
DYSMENORRHEA, N (%)	33 (71.7)	33 (80.5)	0.341
OLIGO-MENORRHEA, N (%)	5 (10.9)	10 (24.4)	0.536
MENORRHAGIA, N (%)	2 (4.3)	2 (4.9)	0.980
HIRSUTISM, N (%)	1 (2.2)	8 (19.5)	0.011*
INTER-MENSTRUAL BLEEDING, N (%)	1 (2.2)	7 (17.1)	0.024*
DYSPAREUNIA, N (%)	1 (2.2)	13 (31.7)	<0.001*
ASEX SCORE, MEDIAN (IQR)	16 (14–20)	7 (6–14)	<0.001*
SEXUAL DYSFUNCTION, N (%)	19 (41.3)	3 (7.3)	<0.001*

CZP – Carbamazepine, LTC – Levetiracetam, SD – Standard Deviation, N – Number, ASEX – Arizona Sexual Experience Scale, IQR – Inter-Quartile Range, *Statistically significance.

Table 3
Hormonal profile of participants.

	CZP	LTC	p-VALUE
Follicular Phase, Median (IQR)			
FSH (mIU/ml)	5.8 (3.3–12.0)	5.5 (3.7–6.5)	0.554
LH (mIU/ml)	6.5 (4.4–15.5)	6.3 (4.3–8.7)	0.560
Progesterone (ng/ml)	0.8 (0.4–4.2)	1.5 (0.9–10.0)	0.056
Estradiol (pg/ml)	68.9 (44.6–110.7)	85.2 (68.9–169.0)	0.061
Luteal Phase, Median (IQR)			
FSH (mIU/ml)	5.6 (2.8–10.4)	5.6 (3.7–6.5)	0.766
LH (mIU/ml)	7.4 (4.5–16.3)	5.0 (3.6–6.5)	0.006*
Progesterone (ng/ml)	0.8 (0.6–4.1)	1.5 (0.7–17.6)	0.142
Estradiol (pg/ml)	71.5 (46.1–128.5)	80.0 (53.7–144.9)	0.540
TESTOSTERONE (nmol/L)	1.0 (0.8–1.8)	1.8 (1.2–2.3)	0.004*

CZP – Carbamazepine, LTC – Levetiracetam, FSH – Follicle Stimulating Hormone, LH – Luteinizing Hormone, IQR – Inter-Quartile Range, *Statistically significance.

Table 4
Quantile regression for testosterone.

	25 Quartile RHO (*P*-VALUE)	50 Quartile RHO (*P*-VALUE)	75 Quartile RHO (*P*-VALUE)
MEDICATION CLASS	0.17 (0.034)	0.12 (0.221)	0.16 (0.424)
AGE	−0.03 (0.030)	−0.05 (0.009)	−0.07 (0.003)
BMI	−0.02 (0.546)	−0.002 (0.933)	−0.05 (0.342)
WAIST CIRCUMFERENCE	0.01 (0.300	−0.002 (0.835)	0.03 (0.206)
NHSS-3 SCORE	−0.01 (0.485)	−0.001 (0.937)	−0.02 (0.557)
ZUNG SCORE	−0.02 (0.263)	−0.02 (0.240)	−0.01(0.736)
ETIOLOGY	−0.04 (0.369)	−0.02 (0.724)	−0.03 (0.712)
REGULAR MEDICATION	−0.17 (0.524)	0.18 (0.538)	0.37 (0.420)

R2: 0.166, R2: 0.218, R2: 0.215.
BMI – Body Mass Index, NHSS – National Hospital Seizure Severity.

AED type was only significant for 25th quantile with those on LTC having higher values compared to those on CZP. This may be important in postulating that there are more reason for lower level of testosterone beyond the inducing effect of CZP leading to lower level of testosterone in WWE and its attending effect. We thus postulate that our findings may be explained by the disruption of regulation of the Hypothalamic-Pituitary-Ovarian axis (HPO) either by chronicity, severity, frequency of seizures, and AEDs. The HPO axis regulation is affected by the abnormal neurophysiology of seizures, and the HPO associated hormones are affected by medications used to treat seizures in WWE.(Harden and Pennell, 2013) Earlier studies had demonstrated a reduction in symptoms and signs of Polycystic Ovarian Syndrome (PCOS) among WWE taking enzyme inducing AED which may explain the lower PCOS symptoms in this study [2,11]. Testosterone levels were lower in the CPZ arm compared to the LTC arm, a contrast was noticed with regards to sexual dysfunction assessment with higher ASEX score indicating poorer sexual function in the CZP arm among WWE from this study. This finding is in tandem with previous separate studies by Mattson and Reimers where presence of sexual dysfunction, decreased sexual satisfaction and decreased libido were demonstrated in WWE taking enzyme inducing AEDs like CZP [14]; Reimers et al., 2015) Testosterone is neuro-protective and enhances adult neurogenesis by increasing the survival of newly generated neuron with minimal influence on cellular proliferation. The neuronal survival described has been linked to either androgen or estrogen dependent pathway that can modulate neurogenesis in females. Activation of MAPK, modulation of BDNF, reduction in impaired neurogenesis effects of stress hormone, restoration of cell proliferation and cell survival to basal survival has been linked to the neuro-protective effect of testosterone. It is thus not surprising that testosterone level was higher in the LTC group as LTC is known to have neuro-protective effect. It appears that increasing testosterone level might be one of the neuro-protective mechanism of LTC. While this properties of increasing testosterone and androgen is good for the neurogenesis and neuro-protection, it has negative effect on reproductive endocrine profile in female because of likelihood of hyper-androgenism and PCOS. On the contrary, CZP reduces the likelihood of reproductive endocrine dysfunction by reducing the level of androgen but have negative cognitive effect which has been previously described.

Furthermore, on issue of weight gain, we found no clinically significant difference between BMI of both groups. However, the CZP group had higher waist and hip circumferences compared to LTC group. This agreed with previous studies that drugs like carbamazepine, gabapentin, valproic acid, vigabatrin and pregabalin are known to increase weight gain while levetiracetam, phenytoin and lamotrigine are weight neutral or at worst induce slight weight loss [15,16]. It is pertinent for physician to pay attention to AEDs induced weight changes and its attending effect on response to medication, cardiovascular, cosmetic and untoward effect [17–19]. It is surprising that the mean Zung depression score was higher among the group on CZP compared to those on LTC as this is against finding from previous studies that linked LTC with depression and other psychiatry comorbidities, especially in those with background psychiatry illness [20,21]. There are several factors that could account for this dissent from previous studies, apart from the fact that most of those on CZP had worse severity score, they largely had structural epilepsy which may affect the functions of HPO axis.

In a quick review of available data on pharmacokinetics profile of carbamazepine from 1965 to 2012 by Ghamari et al., CZP was shown to have high protein binding activity, fair bioavailability which ranges from 75 to 85%, and completely metabolized with the main metabolite as carbamazepine-epoxide. However, CZP induces its own metabolism, leading to increased clearance, shortened serum half-life, and progressive decrease in serum levels [22]. Though, LTC seems to perform better than CZP with regards to sexual function, depression score, seizure severity as demonstrated, the finding is limited by the fact that most of the patients on CZP had structural epilepsy, in spite of the randomly selection.

This study is limited by inability to differentiate between the acute and chronic effect of both AED on the hormonal changes because of the cross-sectional nature of the study. Furthermore, we only compared LTC with CZP, an AED inducing property without no recall to the other AED with enzyme inhibiting properties. Also, the study recruited only female patients excluding male and the post-menopausal women were also excluded. We however think this study has provided basis for further research question from longitudinal comparison of chronic effect on both AED and the need to compare hormonal effect across different age group from adolescent to post-menopausal WWE. More importantly, a longitudinal study of differential effect of AEDs on hormones will give more concrete evidence of causal relationship and temporal profile. This finding underscores the need for physician to focus and incorporate routine sex steroid and hormones evaluation of reproductive endocrine function in management of WWE to optimize care. If a reproductive endocrine disorder is found, antiepileptic drug treatment should be reviewed to ensure that it is appropriate for the particular seizure type and that it would not contribute to the endocrine problem. The possible benefits of a change in treatment must be balanced against seizure control and the cumulative side effect of alternative agents.

5. Conclusion

LTC seems to perform better than CZP with regards to sexual function, depression score, seizure severity. Furthermore, there is a comparable hormonal profile except for higher testosterone level and lower LH level in the LTC compared to CZP group and age was negatively associated with serum testosterone level. The therapeutic implication of these findings needs to be fully explored.

Ethical approval

This was obtained from joint review board of University College Hospital with assigned number of UI/EC/15/077.

Consent to participate

Participants for this study were fully informed on the research protocol detailing the purpose, method, risks, and benefits of the research. Each of the participant then voluntarily gave a written and well understood informed consent. The consent was translated to the local language for those who did not understand English language and the services of interpreters were employed. Participants were free to decline participation or withdraw from the study at any time without reprisal or loss of benefit. There were sections for the person giving the consent, person obtaining the consent and witnesses in the informed consent.

Consent for publication

All the authors gave consent for publication of this manuscript. The corresponding author shall be Dr Ogunjimi Luqman of the department of Pharmacology and Therapeutics, Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University, Ogun state, Nigeria.

Material and data availability statement

The data will be made available upon reasonable request, the principal investigator, will make the data available.

Source of funding

None.

Author contribution statement

Ogunjimi Luqman, Fatai Fehintola, Yaria Joseph, Ogunniyi Adesola: Conceived and designed the study/experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper. </p>

Murtala Abdullahi, Aderinola Aderonke, Oyebowale Mariam, Dada Olaide, Alabi Akinyinka: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper. </p>

Falujo Bolanle, Osalusi Bamidele, Oyenuga Ibironke: Performed the experiments; Analyzed and interpreted the data; Wrote the paper. </p>

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We acknowledge Miss Onafowokan Kanyinsola and Stella for their assistance in data collection.

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