

# Cosmetic effects of Anti-epileptic drugs ( AEDs)

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## Abstract

**Objective :** Adverse effects are leading causes of treatment failure with antiepileptic drugs(AEDs).We studied the cosmetic effects of AEDs and their association with medications adherence and quality of life . **Methods :** The study was performed on Sudanese epilepsy patients attending Daoud charity (June-September2014).Five main variables were used(1)Cosmetic effects profile;(2)Morisky Medication Adherence Scale(MMAS-8);(3)WHO Quality of Life Brief-26;(4)Socio-demographic data,and (5)Epilepsy related data. A senior neurologist assessed the cosmetic effects through clinical examination of the patients. Consents have been obtained from all patients. **Results:** Out of 420 patients male were (54.15%) and female were (45.85%),mean age 34.1±10.4 years. Hair loss was the most commonly reported cosmetic effect by female patients (75%) who were taking sodium valproate.(26.2%)of patients had weight gain and none of them thought weight gain is an adverse effect. Neither of life score, nor adherence score were correlated with any of the cosmetic effects of AEDs ( $P>0.05$ ).A significant positive correlations was found between the duration from the last attack and the quality of life score ( $P=0.03$ ). The Gum overgrowth was correlated with hirsutism and Acne( $P>0.05$ ). **Significance :** We concluded that our patients prioritize medications intake in spite of the presence of cosmetic effects, and this-together with absence of association between quality of life and the cosmetic effect-may be attributed to different Sudanese patients perception to these cosmetic effects from other populations in addition to the unique Sudanese culture.

## Cosmetic effects of Anti-epileptic drugs ( AEDs)

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**Results :** Out of 420 patients male were (54.15%) and female were (45.85%),mean age 34.1+-10.4 years. Hair loss was the most commonly reported cosmetic effect by female patients (75%) who were taking sodium valproate.(26.2%)of patients had weight gain and none of them thought weight gain is an adverse effect. Neither of life score, nor adherence score were correlated with any of the cosmetic effects of AEDs ( $P>0.05$ ).A significant positive correlations was found between the duration from the last attack and the quality of life score ( $P=0.03$ ). The Gum overgrowth was correlated with hirsutism and Acne( $P>0.05$ ).

**Significance :** We concluded that our patients prioritize medications intake in spite of the presence of cosmetic effects, and this-together with absence of association between quality of life and the cosmetic effect-may be attributed to different Sudanese patients perception to these cosmetic effects from other populations in addition to the unique Sudanese culture.

## Key Points:

1. Cosmetic effects of AEDs are of particular concern among women because they can damage body image and self-esteem.
2. Adverse effects of antiepileptic drugs (AEDs) are common, can have a considerable impact on quality of life and contribute to treatment failure
3. Women are more likely to experience Cosmetic side effects (CSEs) compared with men.
4. Epilepsy has diverse effects on the overall wellbeing or subjective quality of life (QOL) of the patients.

## Background

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.<sup>1</sup>The definition of epilepsy requires at least one seizure and evidence of persistent changes in the brain, which increases the likelihood of seizures in the future. The prevalence of men is slightly higher than that of women. <sup>1, 2</sup>The International League against Epilepsy (ILAE) Commission on Classification and Terminology, classify seizures into: Focal seizures that can be further described as having motor, sensory, autonomic, cognitive, or other features, Generalized seizures that can be subdivided into: Absence (Typical, Atypical), Tonic clonic, Clonic, Tonic, A tonic, Myoclonic, and Types that may be focal, generalized, or unclear (Epileptic spasms). <sup>1</sup>In most surveys, approximately 60% of epilepsy will have

no identifiable cause, the main Investigations of a patient with suspected epilepsy are: Electroencephalography (EEG) and neuroimaging (MRI, SPECT, and PET).<sup>2</sup>The management of patients with epilepsy is both challenging and rewarding, The main goal of AEDs therapy is to eliminate seizures without causing side effects.<sup>3</sup>Since 1960s and 1970s sodium valproate (valproate) and carbamazepine became the standard treatments for epilepsy, which they still are.<sup>4</sup>The introduction of new AEDs and the increased emphasis on maximizing the quality of life for patients with epilepsy have led to a new set of goals for the treatment of seizures. These goals have evolved from complete control of seizures, whether side effects occurred, to enabling patients with epilepsy to lead lifestyles consistent with their capabilities.<sup>3</sup>The choice of AEDs following a new diagnosis of epilepsy can be complex and is affected by age, co-morbidity, concomitant medication, possibility of pregnancy and the individual's epilepsy classification.<sup>4</sup>Treatment usually starts with one drug at a low dose. The dose is then increased slowly. In most patients, epilepsy remits over a period of years and drug therapy may be withdrawn slowly.<sup>5</sup>The principal antiepileptic drugs used to treat patients with epilepsy are carbamazepine, ethosuximide, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, primidone, tiagabine, topiramate, valproate, and zonisamide.<sup>6</sup>Current guidelines recommend valproate (VPA) as a treatment of first choice for patients with generalized onset seizures whilst carbamazepine (CBZ) is recommended as the first line treatment for patients with partial onset seizures.<sup>7-8</sup> Several terms are used to describe health problems reported by patients taking AEDs, e.g. "adverse events," "adverse effects," "side effects" and "adverse drug reaction". These terms are often used interchangeably, but they are not.<sup>9</sup> World Health Organization (WHO)'s definition of an adverse drug reaction, which has been in use for about 30 years, It is "a response to a harmful and unexpected drug, and it occurs at a dose that humans usually use to prevent, diagnose, or treat disease or change physiological functions."<sup>10</sup>The terms "adverse reaction" and "adverse effect" are interchangeable, except that an adverse effect is seen from the point of view of the drug, whereas an adverse reaction is seen from the point of view of the patient.<sup>11-9</sup>There are several ways in which adverse effects have been classified. The classification "dose-related" or "idiosyncratic" is most commonly used.<sup>12</sup>Adverse effects are a leading cause of treatment failure with antiepileptic drugs. Not only do they cause 25% of patients to stop treatment prematurely, they also prevent a fully effective dose from being reached and impair patient compliance with treatment.<sup>13</sup>Furthermore, adverse effects of antiepileptic drugs are a major source of disability, morbidity, and mortality.<sup>13</sup>The main reason for changing AEDs is lack of efficacy, but significant side effects are also an important reason for modifying treatment in those patients who reported higher levels of discomfort.<sup>14</sup> With certain modification on the definition of the international conference on harmonization Guideline (ICH) E2A, we can define "cosmetic effect" as any negative (unfavorable) effects or positive (favorable) effects on the beauty, that is associated with the use of a medicinal product, Provided that a causal relationship between them is at least a reasonable possibility. A previous studies done showed the adverse effects of anti-epileptic drugs in the self-administered Adverse Event Profile tend to segregate into five classes. These include 1) Cognition/Coordination (unsteadiness, double or blurred vision, difficulty in concentrating, shaky hands, dizziness, and memory problems); 2) Mood/Emotion (feelings of aggression, nervousness or agitation, and depression); 3) Sleep (tiredness, restlessness, upset stomach, sleepiness, and disturbed sleep); 4) Weight/Cephalgia (weight gain and headache); and 5) Tegument/Mucosa (hair loss, problems with skin, and trouble with mouth or gums).<sup>15</sup>The two classes of Tegument/Mucosa and Weight/Cephalgia with exclusion of headache can be regarded as cosmetic effects.<sup>16-17, 18</sup> Weight gain and loss of hair commonly occur with sodium valproate while loss of weight occurred with levetiracetam. Gum hypertrophy, hirsutism and acne are famous side effects of phenytoin. carbamazepine, phenytoin, phenobarbital, and lamotrigine can cause maculopapular rashes.<sup>18</sup>

## Objectives

### General Objectives:

To assess the cosmetic effects of AEDs among adult Sudanese patients with epilepsy.

### Specific Objectives:

To assess the impact of the cosmetic effects of AEDs on the quality of life.

To assess the correlation between the cosmetic effects of AEDs and the compliance with the medications.**Methodology**

**Study design:** this was prospective cross-sectional, Descriptive study.

**Study area:** Subjects with epileptic seizures were randomly recruited from Banat charity Neurological Referral Clinic.

- Location: Sudan, Omdurman, Omdurman south ( Coordinates: 15°39'N 32deg29'E )
- Sudan is now the third largest country in Africa and also the third largest country in the Arab world (estimated population is little over 30 million people)
- Omdurman is the largest city in Sudan and Khartoum State, lying on the western banks of the River Nile, together With Khartoum and Khartoum Bahri; it forms the cultural and industrial heart of the nation.
- Banat charity Neurological Referral Clinic is a charity clinic, in which neurologists, psychiatrists, physicians, and medical registrars tend to see patients every week at Friday, which is the weekend, and many patients attend this clinic; they are from Khartoum state, but also many of them from deferent states of Sudan. Also the clinic is attended by medical students.

**Study population:** Patients who attend Banat charity Neurological Referral Clinic.

- Inclusion Criteria: includes 1) Age [?] 18 years; 2) History of [?]1 unprovoked seizure; 3) Nationality: Sudanese; 4) Patient with epilepsy who attend Banat charity neurological referral clinic.- **Exclusion Criteria:** Patients that attend Banat charity neurological referral clinic who are non-epileptic or male patients with epilepsy. OR 1) Age < 18 years; 2) History of <1 unprovoked seizure; 3) Patients who is taking other drugs that can cause the same cosmetic effects

**Study duration:** 6 month ( Mar - Aug 2014).

**Sampling:**

**Sample technique:** Simple random sampling /comprehensive non-Probability sampling (Convenient sampling.).

Sample size is the total number during the study period

**Data collection: Data collection and Tools:** Interview with Pre-tested Questionnaires. For each subject, the following data was collected: age, marital status, occupation, residency, educational level, employment, age at seizure onset, seizure type, etiology, and number of seizures before enrollment, history of febrile seizures, and AEDs type and dosing, cosmetic effects, and compliance with treatment.

- The Quality of Life in Epilepsy Inventory (QOLIE)-31.
- World Health Organization (26 items) QOL instrument (WHOQOL-brief).
- The Beck Depression Inventory (BDI) (Psychiatrist interview (Interviewer are a Psychiatric registrars)?
- All interviewers are doctors graduated from faculty of medicine, or a 5<sup>th</sup> year medical student and above.
- **Data analysis:** All collected data were entered into the computer using the statistical package program for social science (SPSS) to analyze the data via simple descriptive statistics. (Analyzer is specialized personnel in SPSS).
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- **Ethical concern:** Written and verbal onsent was obtained from all patients, and ethical approval was obtained from the State Ministry of Health
- **Limitations of the study:**
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Short duration of the study.

The drug serum levels will not be obtained

## Results:

Out of 420 patients', male (54.15%) and female (45.85%). Regarding age distribution mean age 34.1+-10.4 years. In (67%) of our studied group no cause was identified. It was found that (86.4%) of our patients had generalized Epilepsy while (13.6%) had focal Epilepsy. It appeared that (90%) of patients with generalized convulsion showed no abnormality on clinical examination. (50%) of patients with focal Epilepsy showed abnormal neurological manifestations, Almost (64.8%) showed abnormal EEG. The study showed that (90%) of patients with generalize epilepsy had a normal MRI of the brain. Those who had focal epilepsy, (50%) had abnormal MRI of the brain. Sodium valproate, carbamazepine, lamotrogine, levetiracetame, phenytoin, phenobarbitone were the drugs used to be taken by our patients.

Cosmetic side effects occurred in 20% of our studied group (84 patients). Hair loss was the most commonly reported cosmetic effect by female patients (8.2% p0.001 ) who were taking sodium valproate. (8.1 %,p0.001) of our patients had weight gain, weight gain was most frequently associated with valproic acid. Gingival hyperplasia, hirsutism and acne were the most commonly reported in patients taking phenytoin (2%,p0.001). One of our patient who used to take lamotrogine had loss of weight. One patient on phenobarbitone and one on carbamazepine had skin eruption. Cosmetic side effects leading to dosage change or discontinuation occurred most frequently with sodium valproate compared with all other AEDs (2.3% P 0.001). Neither of life score, nor adherence score were correlated with any of the cosmetic effects of AEDs (P>0.05). A significant positive correlations was found between the duration from the last attack and the quality of life score (P=0.03).

## DISCUSSION

Epilepsy is a relatively common condition characterized by a tendency for recurrent seizures, which is due to the disturbance of spread of electrical discharge of the cortical neurons.<sup>19</sup> Epilepsy is either: idiopathic when there is no underlying cause or secondary if there is an underlying cause e.g. brain tumors, stroke. Clinically seizures are divided into two basic categories, generalized and focal. As many as 80% of epilepsy patients can be controlled with anti-epileptic drugs. The type of medication prescribed depends on the type of seizure, the underlying cause of the epilepsy, the age of the patient, possible side effects, and the availability of the medication. Treatment usually starts with a low dose and then gradually increases. In most patients, the epilepsy will subside after a few years and medications can be stopped gradually.

Phenytoin is effective for the treatment of focal and tonic clonic seizures. Carbamazepine is effective in the treatment of focal and generalized tonic-clonic seizures, while phenobarbital is as effective as phenytoin and carbamazepine in clearing focal and generalized tonic-clonic seizures. On the other hand, sodium valproate is effective for all types of epilepsy patients. The occurrence of adverse effects unrelated to the dose, is particularly prominent during the initiation of therapy (especially with carbamazepine and valproic acid), but disappear as tolerance develops. For this reason, therapy with these drugs should be started on low doses and the dose slowly titrated up to the recommended maintenance over several weeks.<sup>20</sup>

Cosmetic effects of AEDs are of particular concern among women because they can damage body image and self-esteem. Adverse effects of antiepileptic drugs (AEDs) are common, can have a considerable impact on quality of life and contribute to treatment failure in up to 40% of patients. Women are more likely to experience Cosmetic side effects (CSEs) compared with men. Like what was reported by other researchers' worldwide cosmetic side effects (CSEs) such as weight gain and alopecia are common among our studied group and occurred commonly among patients taking sodium valproate.<sup>21</sup> Current guidelines recommend valproate (VPA) as a treatment of first choice for patients with generalized onset seizures. Weight gain is a known dose-related side effect of valproic acid that more commonly is seen in women. Polycystic ovary disease and hyperandrogenism are common in women taking valproate. Hyperandrogenism presents as hirsutism, acne, or male-pattern alopecia. Other AEDs, such as felbamate and topiramate, are associated with significant weight loss, occasionally requiring discontinuation of the AEDs. Like what was mentioned in

the literature phenytoin causes excessive hair growth, particularly on the face and arms, as well as facial acne and coarsening.<sup>21</sup>Gingival hypertrophy was reported in 13% of persons taking phenytoin.

Like what was mentioned in the literature maculopapular rashes were noted in 3% of our patients started on carbamazepine, phenytoin, phenobarbital, and lamotrigine.<sup>22</sup>Rarely severe mucocutaneous reactions such as Stevens-Johnson syndrome, and toxic epidermal necrolysis can occurred with the use of these antiepileptic drugs. <sup>23</sup>Patient taking phenobarbital can have many skin reactions, including: morbilliform, urticaria, erythema multiforme, photosensitivity, acneiform rash, and purpura. Skin eruptions are significantly more likely if lamotrigine is given with valporic acid, especially if the recommended dose is exceeded. Adverse effects of Lamotrigine may include serious toxic epidermal necrolysis, in which alopecia is a well-known phenomenon. The occurrence of carbamazepine-induced alopecia is at or below 2%.<sup>24</sup>Hair loss is a side effect of patients taking aromatic anticonvulsants, but it rarely occurs after such drugs are discontinued during recovery from anticonvulsant hypersensitivity syndrome. <sup>24</sup>

Epilepsy has diverse effects on the overall wellbeing or subjective quality of life (QOL) of the patients.<sup>25</sup> QOL in epilepsy is associated with several factors. These factors include clinical variables (for example, seizure frequency, severity, illness duration, treatment side effects and psychiatric co- morbidities), social disadvantages (for example, divorce, unemployment, social stigma, and illness intrusion into social life), and family circumstances (such as family caregiver characteristics and social support).<sup>25</sup> Adverse effects of antiepileptic drugs have emerged as one of the strongest predictors of impaired health-related quality of life, independent of seizure outcome. <sup>26</sup>

## **Declarations:**

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

The materials datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

### **Competing interests**

The authors declare that they have no competing interests.

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### **Authors' contributions**

All authors participated in planning the study, data collection, results and discussion sections.

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**We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.**

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