

## Reproductive Health, Social and Financial Impact of Valproic Acid Withdrawal for Childbearing Epileptic Saudi Woman

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### Abstract

Epilepsy complicates a woman's reproductive life. The physiological modification of the woman and the effects of antiepileptic drugs are generally the cause. Several complications may be added during treatment that requires careful monitoring. The risks in women of childbearing age associated with prenatal Valproic Acid Drug (VPA) exposure are becoming established, and updated recommendations are being made internationally for restrictions to (VPA) use and enhanced preconception counseling in this patient group.

To minimize these complications we implement same protocol in the different hospital departments to assure high quality of care for childbearing age women. As a result we remark a decrease number of patients using (VPA) and improvement of the quality of reproductive health and per consequence reducing hospital and societal costs.

**Keywords:** Childbearing age women; Epilepsy; Valproic acid; Depakin complication; Hospital and social cost

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### Introduction

Being a woman with epilepsy is not the same as being a man with epilepsy. Epilepsy affects sexual development, menstrual cycle, aspects of contraception, fertility, and reproduction. Epilepsy causes significant medical and social costs, and places an economic burden on society and individuals by causing increases in healthcare costs, as well as losses in employment, wages and household work [1-3]. (VPA) interferes with the endocrine system at multiples levels causing several reproductive and sexual dysfunctions in women with epilepsy [2,4].

It is now not recommended that (VPA) should be prescribed routinely for women with child-bearing potential. If (VPA) use is inevitable, then recommendations are for a clinical discussion involving teratogenic risk, pregnancy planning, and contraception advice [5-7].

NICE 2021 advice a special consideration for women and girls with epilepsy and prepare a special pathway to manage during the child-bearing period [8]. The main objective of our study is to provide health promotion, screening and interventions to epileptic women of childbearing age using (VPA) before conception and thereby improve pregnancy-related outcomes.

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### Method

This study was carried out after the establishment of a similar management protocol in all the departments that take care of epileptic patients of childbearing age (Figure 1).

We are interested in calculating only the cost of laboratory tests and radiological examinations necessary to investigate the potential indisputable effects of (VPA) and the costs of pharmaceuticals as preliminary project. The cost of admissions,

visits by general practitioners and specialists, have not been calculated on the one hand because it is a preliminary study and on the other hand these management are offered free of charge in our hospital.

A same protocol has been implemented in the different departments involved in the management of a child-bearing epileptic patient (since the age of 9 years to 45 years old) (Figure 1). All female patients with diagnosis of epilepsy (OPD, pediatric clinic and gynecology clinic) are referred to neurology clinic.

Once the patient visits a neurology clinic the neurologist will take from history some focus information's (general information, questions about treatment given for epilepsy, problems related to period, sterility problem, planning for pregnancy). The patient switched to another antiepileptic progressively if the patient is initially was on (VPA). The patient who are on (VPA) and they plan for pregnancy or have problem to get pregnant should be seen by gynecology for laboratory investigation and pregnancy planning.

Each year we calculated the number of patient using (VPA), endocrinology problems resolved and the cost of treating reproductive health problems. We chose as direct cost only the blood tests and the radiological exams requested to explore the side effects of (VPA). Investigations done to have diagnosis are the same for all epileptic patients in our hospital that is why we did not include these parameters in our study. Drug costs were based on the year 2017 acquisition cost of drugs by the hospital. Total drug costs were then calculated using the unit prices and duration of prescriptions.

### Ethical considerations

Ethics committee review was not required for this project as it was a quality improvement project for already existing practices and treatments in the hospital.

### Results

Between November 2017 and October 2021, the total number of female epileptic patients was 269. Patients who are on child-bearing period (9-45) were 125. Initially on 2017, 45 Patients were on (VPA) (36%), the others patient were on Lamotrigine (20) 16%, Carbamazepine (28) 22.4%, Leviterecitam (36) 28.8% and (9) 7.2% on Phenytoin (Figure 2).

2021 only two patients were on VPA. One of them was Down syndrome and she is on bi-therapy the other one is cerebral palsy. The following diagram (Figure 3) summarizes the various undesirable effects observed in epileptics patients treated with VPA. In our study we are only interested in the cost directly related to the side effects caused by VPA (Figures 4 and 5).

### Discussion

Epilepsy is an important public health issue in many countries. The prevalence of this disease is estimated between 5 and 9.3/1,000, with a predominance feminine of the period from 10 to 14 years [5]. Sub fertility and sexual disorders in epileptic patients are known and have been described for the first time in 1954 by Gastaut and Collomb Epilepsy causes significant medical and social costs, and places an economic burden on society and

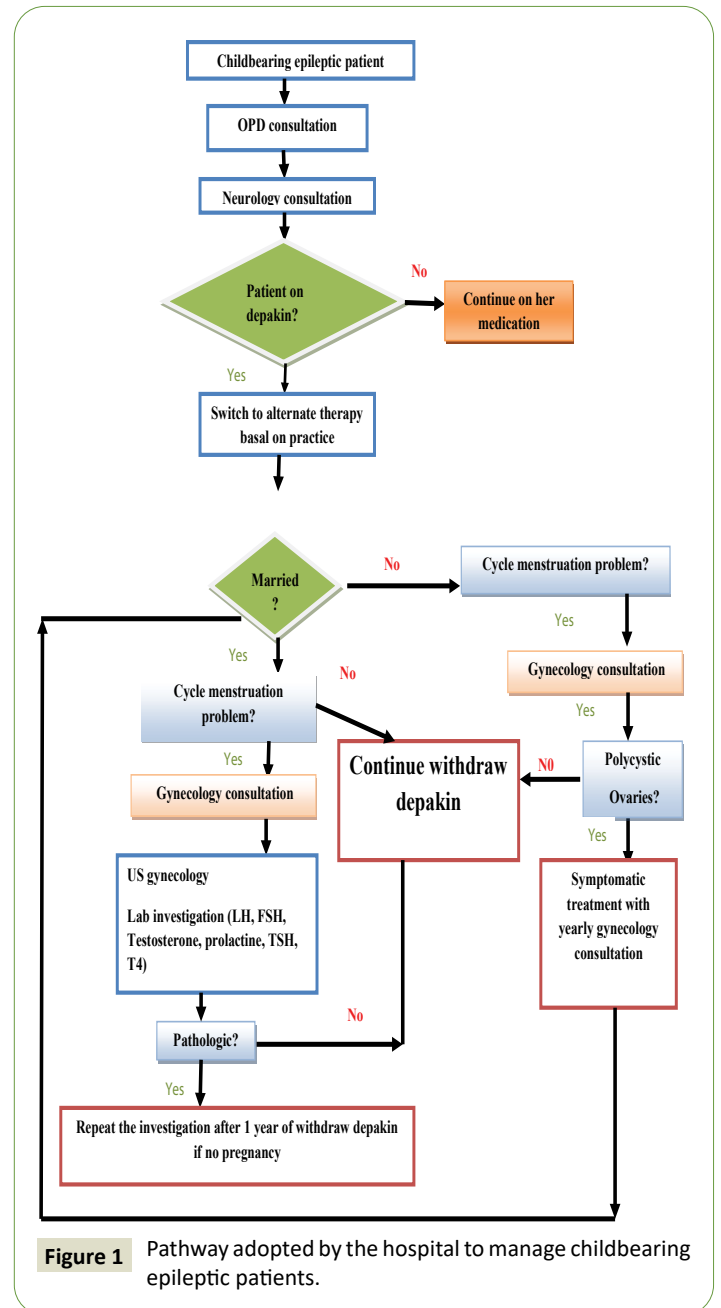


Figure 1 Pathway adopted by the hospital to manage childbearing epileptic patients.

individuals by causing increases in health care costs, as well as losses in employment, wages and household work [8].

Little information is available with regards to epilepsy and antiepileptics drugs (VPA) complication in Saudi women with epilepsy. The particularity of our study is to show the improvement of the reproductive health of epileptic patients under (VPA) after the gradual withdrawal of this antiepileptic in patients of childbearing age and then calculate the cost saving to the hospital after adequate management from the onset of the disease of patients with epilepsy. The current study found a decline in the rate of prescription of (VPA) between 2017 and 2021 from 36% to 1.6%.

On 2017, 26% of our patients who are on (VPA) have experience abnormalities in menstrual cycle, 26% have problems to get pregnant and 15% of them have the diagnosis of Polycystic Ovary

may change serum concentrations of reproductive hormones in patients with epilepsy, thus contributing to the development of reproductive dysfunction [5]. In our study 26% of our patients have problems to get pregnant and 41% (5 patients) of them the hormonal check-up was pathologic.

Endocrine problems were clear in our population. A Filnandan study followed 35 epileptics women aged 12-25 years for an average of 5.8 years who received (VPA). All of these women had hyper-androgenia, 63% had (PCOS), increased blood levels of prolactin, hormones secreted by the pituitary and hypothalamus [11].

Laboratory measurements include serum levels of PRL, LH, FSH, testosterone, GnHR and thyroid hormones are indicated to epileptic women on (VPA) with irregular menstrual or difficulty to get pregnant [5]. Two of our patients were switched to Lamotrigine and 2 years after they have their first baby. One of them was programmed to an artificial insemination but she get pregnant spontaneously only by withdraw (VPA). The same result was found in another study when they switch from (VPA) to Lamotrigine. They remarked reversal of hyper-androgenism, and normalization of ovarian morphology [12].

Once improving reproductive health in women of childbearing age remains the primary goal of any health system, it becomes necessary to identify and address the various obstacles. This is why economic analysis is an indispensable tool in the promotion and production of preventive therapies and effective strategies for different diseases and in particular those with a heavy social and economic burden such as epilepsy.

We study only the direct cost of (VPA) complications in child bearing epileptic female patients. We found that when we shift patients from (VPA) to another safe treatment we gain 90.000 RS (only for 45 patients) that is mean 2.000 RS per patient and per years.

We should know that our cost include only cost of medication, laboratory and gynecologic ultra sound requested to investigate gynecologic problems. We have chosen to study the treatment cost in childbearing age patient because this age range is important in the improvement of reproductive health.

The majority of publications talk about the undesirable effects of (VPA) and its cost on pregnancy and newborns [13], but the

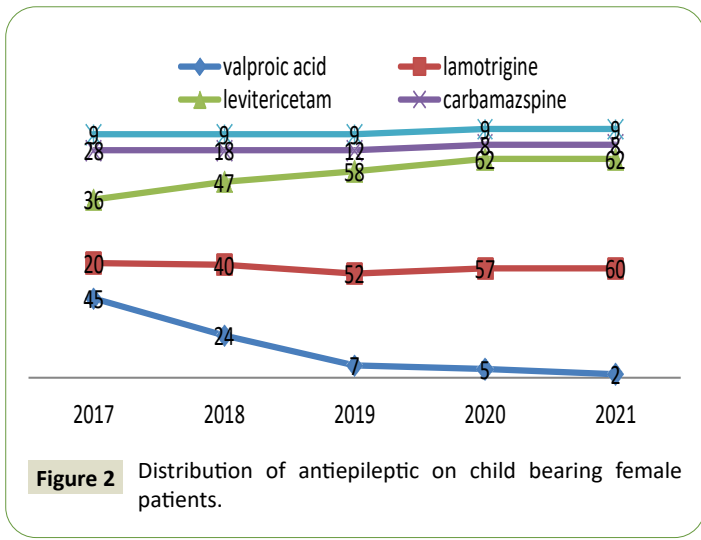


Figure 2 Distribution of antiepileptic on child bearing female patients.

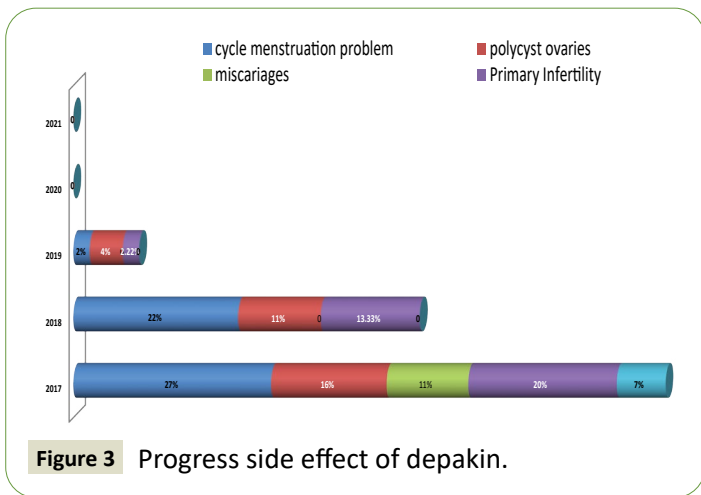


Figure 3 Progress side effect of depakin.

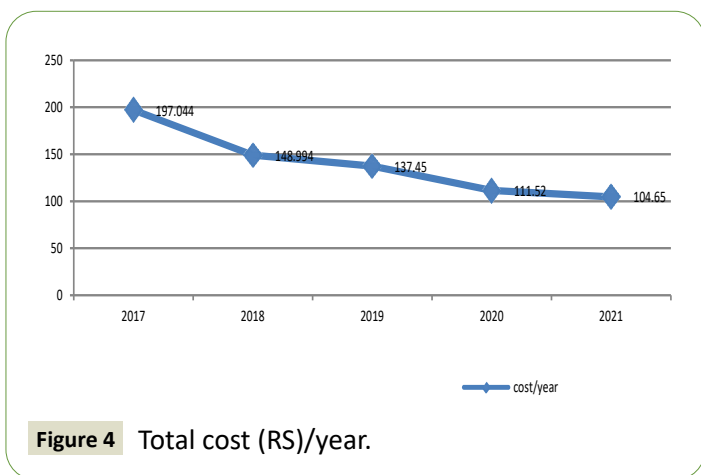


Figure 4 Total cost (RS)/year.

Syndromes (PCOS). One study reports that ovulation was delayed in women with epilepsy [9]. Another study published on 2012 conclude that there is an increased incidence of PCOS in Chinese women with epilepsy at reproductive ages, by more than 2 times of that in the general population. Risk factors include seizures starting at a young age and (VPA) therapy [10].

Actually is well known that antiepileptic Drugs, particularly VPA,

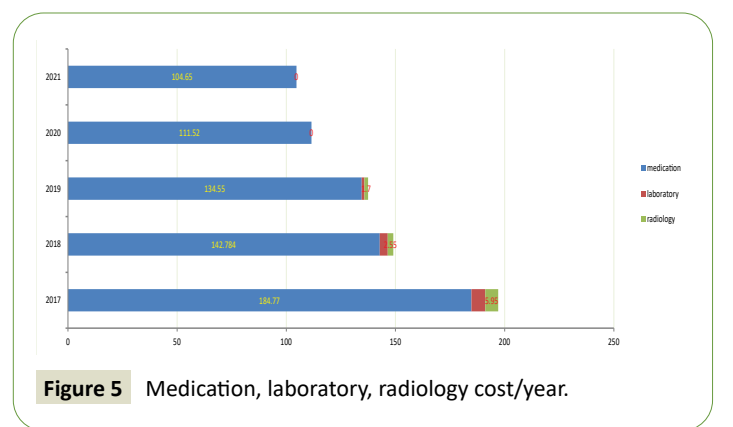


Figure 5 Medication, laboratory, radiology cost/year.

possibility of preventing these damages from an early age in epileptic women of childbearing age is not clearly mentioned in literature.

The gain was significant despite the fact that our patients were put on the new antiepileptic which is more expensive than the old antiepileptic. This shows that an early catch can prevent this burden [14]. The cost of hospitalization, visits by specialists and family doctors have not been calculated because they are provided free of charge to our hospital.

The indirect cost that is not calculated in our study and has been mentioned in other studies [15], such as lost days of work, psychological and family comfort felt by our patients. These studies looking at the direct and indirect cost of epilepsy have shown that the indirect cost is at least 58% of the total cost [3,16].

In addition, the majority of our patients were students or women working. We have seen an improvement in their productivity and a clear decrease in demand for sick leave during consultation.

## Conclusion

This preliminary study provides the cost data for the treatment

of child bearing female patient in Saudi Arabia. The results can help not only the institution concerned, but also the country as a whole in the appropriate and efficient distribution of health care resources. The results can also provide a useful basis for pharmaco-economic evaluations of interventions, such as those of the new antiepileptic, despite being more expensive than the old antiepileptic (VPA) but providing better protection for this category in terms of reproductive health, quality of life and social and hospital cost.

## Limitation of our Study

A limit of our study is that it is menu on a small population.

The indirect cost that we did not calculate has a large effect on reproductive health outcomes, with a large effect on reducing hospital and social costs.

It is time to pay more attention to this category and to develop a program at the level of the Kingdom to improve the reproductive health of childbearing women because of its repercussions on the economic and the well-being of future mother and descendants.

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