Depression in patients receiving pharmacotherapy for epilepsy

Thesis

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Ahmad Abd-Elmordy

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List of Abbreviations

Abb.	Full term
AED	Antiepileptic Drug
BDI	Beck Depression Inventory
CBT	Cognitive Behavioural Therapy
DBS	Deep Brain Stimulation
DSM	Diagnostic and Statistical Manual for Mental Disorders
ECT	Electroconvulsive Therapy
FDA	Food and Drug Administration
GABA	Gamma Aminobutyric Acid
HADS	Hospital Anxiety and Depression Scale
HPA	Hypothalamic-Pituitary-Adrenal
ILAE	International League Against Epilepsy
NDDI-E	Neurological Disease and Depression Inventory-Epilepsy
NPV	Negative Predictive Value
OR	Odds Ratio
PHQ	Patient Health Questionnaire
PPV	Positive Predictive Value
PWE	Person with Epilepsy
RCT	Randomized Controlled Trial
Se	Sensitivity
Sp	Specificity
SSRI	Selective Serotonin Reuptake Inhibitor
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
TMS	Transcranial Magnetic Stimulation
LAC	Lacosamide

List of Abbreviations Cont...

Abb.	Full term
LEV	Levitacetam
OXC	Oxicarbamazepine
LTG	Lamotrigine
ZNS	Zonizamide
VAP	Sodium valproate
PHT	Phenytoin
CBZ	Carbamazepine
PHB	Phenobarbital
TPM	Topiramate
CLB	Clobazam

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INTRODUCTION AND AIM OF THE WORK

Depression is will known co-morbidity among patients with epilepsy, hypothetical causes that the pathogenic mechanisms are the same to both depression and epilepsy –like neurotransmitter and structure abnormality- and stress burden suffering of seizures and its sequences but one of underestimation factors is anti-epileptic drugs it self what it is the subject of this study.

Timely recognition and treatment of depression is of the essence in epilepsy patients, as its persistence is an independent predictor of poor quality of life, increased suicidal risk, greater use of health services, and higher medical 0costs not related to the psychiatric treatment ***(Fisher et al., 2014).***

The primary objective of the study will to determine the prevalence of depression in epileptic patients on AEDs with Arabic version of neurological disorders depression inventory for epilepsy (NDDI-E).

The secondary objective will to determine the contributing factors like, seizure frequency, seizures control, type of AEDs, number of prescribed AEDs, their regimens, AED load, among these patients.

Epilepsy is a common chronic neurological disorder with around 50 million people world wide have it ***(WHO website – epilepsy).***

Further, patients with epilepsy are generally on multiple antiepileptic drugs (AEDs) which are often associated with behavioral alterations including depression and suicidal ideation ***(Bharucha, 2012).***

The incidence of depression in patients with epilepsy ranges from 20 to 54% which is a cause of concern and is often overlooked or under-recognized ***(Kwan et al., 2009).***

The newer AEDs differ in their mechanism of action from the older agents and also have effect on cognition and mood. There are few reports of suicidal ideation also nevertheless available evidence is insufficient to prove this association ***(Andersohn et al., 2010).***

The psychiatric adverse effects of AEDs are less frequently reported in non epileptic populations which may be due to lower doses of AEDs or due to underlying neurological condition ***(Mula, 2011).***

Epilepsy itself is known to be associated with depression with shared pathology and four to five time greater incidence, some studies have evaluated the relation between them by using various depression scales (***Gilliam et al., 2006).***

However, there is scarcity of literature regarding the prevalence of depression in Egyptian population , Furthermore, these symptoms are sometimes used to be neglected in the routine follow up for the treatment of severe seizures in epilepsy. Thus, the present study was done to evaluate the association of depression between use of AEDs (as an adverse effect), disease process (as estimated by seizure control) and other contributing factors in epileptic patients. Depression will assessed by using Arabic version of The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) is a 6-item questionnaire validated to screen for depression in people with epilepsy which is valid with sensitivity of 93.33% and a specificity of 94.44% were found with NDDI-E total scores equal or > 15 ***(Friedman et al., 2009).***

The positive predictive value was 87.5%, and the negative predictive value was 97.14% ***(Friedman et al., 2009).***

Moreover, this is study to evaluate the depression like symptoms in. Further, the comparison between newer and older AEDs was done to evaluate the difference, if any, in terms of occurrence of depression between different drugs and other factors

Chapter 1

EPILEPSY AND AEDS

The word *epilepsy* is derived from Greek words meaning "to seize upon" or a "taking hold of." Our predecessors referred to it as the "falling sickness" or the "falling evil" ***(Adames & Victors, 2019).***

The operational revised 2014 definition of epilepsy by the International League Against Epilepsy is ***(Fisher et al., 2014):***

1. At least 2 unprovoked (or reflex) seizures occurring greater than 24 hours apart.

2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years.

3. Diagnosis of an epilepsy syndrome.

A seizure is defined as a transient change in the clinical state of the patient due to excessive neuronal firing or depolarization. Seizures can be provoked or unprovoked ***(Singh & Trevick, 2016).***

A seizure can have motor, sensory, psychic, or autonomic manifestations or a combination of these.

Examples of evidence that increases the probability of having additional seizures include:

1. Epileptiform activity on EEG
2. A potential epileptogenic abnormality on brain imaging.

Thus, if the clinical picture, EEG or imaging findings increase the probability of another seizure to ≥60%, then these individuals are defined as having epilepsy, and should be, as clinically they are statistically equivalent in their recurrence risk to those who have had two or more unprovoked seizures ***(Fisher et al., 2014).***

- ***Etiologies***

The ILAE Task Force has defined six etiologic categories, focusing on those etiologies with management implications. These categories are:

1. Structural
2. Genetic
3. Infectious.
4. Metabolic.
5. Immune.
6. Unknown.

These are not hierarchical and more than one might often apply. Further clarification and description of what would fall into these etiologies is as follows:

1) **Structural etiology:** a finding on neuroimaging reasonably inferred to cause the patient's seizures due to concordant EEG and clinical findings ***(Lapalme-Remis and Cascino, 2016).***

An imaging abnormality with discordant seizure semiology and EEG findings is likely unrelated to the patient's epilepsy and would not be considered relevant when determining their epilepsy type ***(Lapalme-Remis and Cascino, 2016).***

2) **Genetic etiology** a specific disease-causing variant in a gene or copy number variant, believed to be pathogenic for epilepsy, would lead to a genetic classification ***(Hildebrand et al., 2013).***

Having a relevant family history and typical features (EEG, seizure semiology) without the molecular genetics is sufficient for a genetic etiology classification ***(Hildebrand et al., 2013).***

Determining when a genetic variant is causative remains challenging, with many patients having variants of unknown significance.

Genetic disease causing variants often arise de novo and are not inherited, so a family history of epilepsy is frequently

not present, despite the patient having a genetic cause for their epilepsy ***(Hildebrand et al., 2013).***

3) **Infectious etiology:** refers to a patient with epilepsy, not a patient with seizures due to an acute infection.

A patient with an acute infection and seizures does not have epilepsy as their seizures are provoked (and thus no epilepsy type classification should be made) ***(Vezzani et al., 2013).***

Infectious etiologies are exemplified by: Neurocysticercosis, HIV, Cytomegalovirus, cerebral toxoplasmosis, many of which could also be considered a structural etiology ***(Vezzani et al., 2013).***

4) **Metabolic epilepsies:** refers to a patient with epilepsy in which the core of the epilepsy is due to a metabolic derangement. Someone with a transient metabolic disturbance resulting in acute-symptomatic seizures would not qualify as their seizures are provoked, and therefore they do not have epilepsy, examples include pyridoxine-dependent seizures and cerebral folate deficiency ***(Parikh et al., 2015).***

5) **Immune etiology:** when an auto-immune disease is the cause of newonset epilepsy. Antibody mediated limbic encephalitis is an increasingly recognized cause of seizures in epilepsy of unknown origin ***(Toledrano & Pittock, 2015).***