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Retrospective Analysis of Nonepileptic Patients With Isolated Epileptiform Discharges Treated With Anticonvulsants

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Abstract

Many antiepileptic drugs (AEDs) have been tested on nonepileptic patients with a variety of diagnoses. The Food and Drug Administration has only approved certain AEDs for a small number of psychiatric conditions. There are few studies of nonepileptic patients that recommend an empirical trial of AEDs when isolated epileptiform discharges (IEDs) are identified in the electroencephalogram (EEG). However, no trials have been published. The purpose of this study is to evaluate the outcome of treating nonepileptic patients with AEDs when IEDs are present. Refractory cases were reviewed from a multidisciplinary practice whose EEG readings contained IEDs and were subsequently medicated with anticonvulsants by the clinic's psychiatrist. The psychiatrist's progress notes were assessed to determine the impact of adding anticonvulsants based on parent reports, teacher reports, and clinical observation. The final sample was composed of 76 refractory cases. Of the 76 patients treated with anticonvulsants, the majority were found to be improved in follow-up progress notes: 65 improved (85.53%), 6 unchanged (7.89%), and 5 more severe (6.58%). These observational findings suggest that further studies will be needed to show that IEDs may predict positive treatment outcome to anticonvulsant medication and act as a step toward an evidence-based treatment. Also, EEG screening may prove to be useful for refractory cases regardless of age, gender, or diagnosis.

Keywords

isolated epileptiform discharges, antiepileptic drugs, electroencephalogram (EEG), nonepileptic patients, psychiatry, research domain criteria (RDoC), precision medicine

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Introduction

Treating nonepileptic patients with antiepileptic medications has been a debate for many years. Standards of practice in neurology dictates that antiepileptic drugs (AEDs) are only used once a person is diagnosed with a seizure disorder following 2 unprovoked convulsions. It is possible that the reason for this avoidance of AEDs is due in part to the high side effect profile of older AEDs such as carbamazepine, valproate, topiramate, and zonisamide. These drugs have been known to cause confusion, sedation, psychomotor slowing, change in cognition, impairment of language/verbal memory, slurred speech, and behavioral or psychiatric adverse effects. The new generation of AEDs have a much lower side effect profile. The slowing of cognitive processes by the older AEDs is no longer seen in the new AEDs such as lamotrigine and oxcarbazepine until one reaches very high doses.[1] Because of the potential negative effects of AEDs there has been controversy in neurology of treating nonepileptic patients with AEDs.

The use of AEDs in psychiatry is much more liberal; many practices use AEDs off-label to treat a variety of symptoms such as mood control issues, aggression, and refractory depression.[2] Lamotrigine has Food and Drug Administration approval for the treatment of bipolar disorder. However, past research investigating the use of AEDs on nonepileptic psychiatric patients has yet to clarify when their utility may be beneficial. There is a paucity of empirical studies providing guidance on the use of AEDs on nonepileptic populations. A trial executed by Davids et al[3] indicated that oxcarbazepine may be beneficial as a treatment of attention deficit/hyperactivity disorder (ADHD) in adults. Ettinger and Argoff[4] assessed studies on the following AEDs: benzodiazepines, valproate, phenytoin, carbamazepine, tiagabine, gabapentin, pregabalin, lamotrigine, levetiracetam, zonisamide, oxcarbazepine, and topiramate. Each of these drugs was assessed based on its impact on a specific diagnosis. In their conclusions, none of these AEDs were found to provide

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significant benefits to their specific targeted behavior. Other research yields similar results.[5-8]

When levetiracetam was compared with a placebo in child and adolescent subjects with autism spectrum disorder, no significant difference was found.[5] Additionally, in a study regarding the treatment of antiepileptics on juvenile bipolar disorder, migraine, and neuropathic pain, data were found to be insufficient to prove effectiveness of these medications on children and adolescents, despite their frequent use.[6] Finally, in a systematic review and meta-analysis of AEDs versus placebos for autism spectrum disorder, AEDs did not appear to have a significant effect size for behavioral related symptoms.[7] Out of the 7 randomized controlled trials, only 1 utilized an electroencephalogram (EEG) to screen for abnormalities instead of relying on only diagnosis. This study by Hollander et al[8] found only 2 of the 17 subjects to have epileptiform activity, both of which responded positively to divalproex sodium for the treatment of irritability. Because of the small sample size, the study was unable to draw conclusions. It is clear that research is needed to evaluate psychiatric usage of AEDs in nonepileptic patients with isolated epileptiform discharges (IEDs).

Technological advancements in the past decade have opened the possibilities of assisting diagnosis and medication selection. One example is the field of pharmacogenomics, which assists in analyzing individual's response to medication based on their genetic characteristics.[9,10] The goal of the National Institute of Mental Health Research Domain Criteria project (RDoC) is to move away from a symptoms-based approach toward an evidence-based approach for diagnosis. They are requesting research that links neurological abnormalities to symptoms assisting in diagnosis and treatment planning. The RDoC has identified EEG as technology that should be investigated as an instrument to assess brain physiology.[11] For example, Arns et al[12] found that EEG abnormalities were associated with nonresponse to escitalopram and venlafaxine-XR, but not sertraline.

In the past, EEGs have commonly been utilized when brain abnormalities were suspected. These included encephalopathies, cerebrovascular issues, tumors, neurological abnormalities, and seizure activity. EEGs are specifically beneficial when they are able to detect abnormalities that would otherwise go undiscovered. IEDs, a form of seizure activity in the brain that does not manifest into convulsion, is an example of this. In past research, IEDs have been found to be highly prevalent in certain psychiatric populations. For example, Millichap et al,[13] and Swatzyna et al[14] found a high prevalence of IEDs in ADHD patients.

IEDs cannot be diagnosed with a symptoms-based approach due to the fact that they underlie many different psychiatric presentations depending on their location in the brain. Although IEDs are considered a normal variant within the general population, they are more prevalent in a psychiatric population.[15-18] Zimmerman and Konopka[19] found that IEDs were associated with increased psychopathology compared with discharges that distribute across hemispheres. IEDs represent a dysregulated focus isolated to one part of the brain that is not likely to develop into a seizure focus but would possibly respond well to an AED intervention. It has been suggested that AEDs be considered when IEDs have been identified,[13,14,20] but there is a paucity of research to confirm this.

In order to verify the efficacy of treating nonepileptic patients with AEDs, past cases in which AEDs were prescribed need to be reviewed. In our multidisciplinary practice, EEGs are commonly utilized when patients fail multiple medication trials. Swatzyna et al[21] identified 4 abnormalities in the majority of medication failure cases: encephalopathy, focal slowing, beta spindles, and transient discharges. In this study, IEDs were a subclassification of transient discharges. When IEDs were identified, regardless of diagnoses, the clinic's psychiatrist in many cases prescribed AEDs. The purpose of this study is to evaluate the symptom outcome when patients with IEDs are prescribed AEDs, regardless of diagnosis. On a chart review, we expect to find a positive response to the introduction of AEDs. This response will be measured by the indication of improvement in the psychiatrist's notes. By finding this, we suggest more research is needed before psychiatry moves toward a more evidence-based approach for treatment. In addition, we propose that EEG could be utilized as part of the medication selection process.

Methods

The data archive (N = 735) was obtained from a multidisciplinary practice that treats a wide variety of neuroatypical patients. Diagnoses were made by board certified psychiatrists and psychologists according to the *DSM-IV-TR* (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision) criteria. The data were collected over a 5-year period for those referred for an EEG assessment. The data archive was submitted to an institutional review board and granted a "waiver of approval" meeting the exemption categories set forth by federal regulation 45 CFR 46.101 (b) (2) and (4).

Patients

Out of 735 cases, 76 were included for the purpose of this study. To fit the criteria, patients had to undergo an EEG that identified IEDs, be treated by the clinic's psychiatrist, and subsequently medicated with AEDs. An AED treatment plan would often entail removing any medications that lower seizure threshold and adding an anticonvulsant, such as oxcarbazepine or lamotrigine. Patients were eliminated if they were diagnosed with a seizure disorder, treated outside of the practice, or prescribed AEDs at the time of the EEG. The study included 61 males (85.53%) and 15 females (19.74%), age range 5 to 52 years. Demographics were distributed as: 35 children aged 5 to 12 years, 17 adolescents aged 13 to 18 years, 13 young adults aged 19 to 25 years, and 11 adults aged 26 to 52 years.

Table 1. Demographic Distribution of Reported Symptom Change After Antiepileptic Drug Prescription.[a]

	Improved, % (n)	No Change, % (n)	Worse, % (n)	Group Totals, n
Children: 6 female/29 male	91.43 (32)	5.71 (2)	2.86 (1)	35
Adolescents: 2 female/15 male	76.47 (13)	11.76 (2)	11.76 (2)	17
Young adults: 3 female/10 male	76.10 (10)	7.70 (1)	15.38 (2)	13
Adults: 4 female/7 male	90.91 (10)	9.09 (1)	0 (0)	11
Percentage totals	85.53 (65)	7.89 (6)	6.58 (5)	76

[a]Categories are divided by the following age groupings: children aged 5 to 12 years, adolescents aged 13 to 18 years, young adults aged 19 to 25 years, and adults aged 26 to 52 years. Numbers in parentheses after percentages represent the numerical distribution within the demographic categories.

EEG Data Acquisition and Analysis

EEG acquisition was performed using Mitsar-EEG-10/70-201 equipment, with impedance maintained below 10 kohm. The patients were seated in a slightly reclining chair in a silent and low light environment. Electrocap was used to collect the data according to the international 10-20 system with linked ears montage (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). A minimum of 20 minutes of total data were recorded in both eyes open (10 minutes) and eyes closed (10 minutes) resting conditions. The order of these could vary among patients.

All EEG data were evaluated and interpreted by the same neurophysiologist, a member of the American Board of Electroencephalography and Neurophysiology and the American Board of Clinical Neurophysiology. Visual inspection of the EEG was performed in order to search for paroxysms.

Procedure

Once IEDs were identified the psychiatrist prescribed one of the following AEDs: oxcarbazepine, lamotrigine, gabapentin, valproic acid, or ethosuximide. A retrospective chart review was conducted for the 76 patients who met all inclusion criteria. Once IEDs and AEDs were indicated in the data archive, the patient's charts were pulled in order to view the psychiatrist's progress notes. In the notes following the prescription of AEDs, the patient's symptoms were placed into 1 of 5 categories: resolved, much improved, less severe, no change, or more severe. The psychiatrist used parent and teacher reports and his or her clinical observations to rate each patient. The "much improved" rating was based on all 3 raters agreeing on "much improved." A "less severe" rating was given when 2 out of 3 raters noted improvement. Once the ratings were identified, they were collected and documented in a spreadsheet.

Results

Out of the 76 patients who were put on AEDs, the symptoms of 1 (1.32%) was resolved, 34 (44.74%) much improved, 30 (39.47%) became less severe, 6 (7.89%) experienced no change, and 5 (6.58%) became more severe. In total, 85.53% of the patient's symptoms experienced a positive change (resolved, much improved, or less severe) after the application of an AED. Further demographic distributions of reported symptom change are provided in Table 1.

The AEDs that seemed to have the best reaction were lamotrigine and oxcarbazepine, whereas gabapentin, divalproex sodium, and ethosuximide were prescribed less (lamotrigine = 45.45%, oxcarbazepine = 41.55%, gabapentin= 9.08%, divalproex sodium = 2.59%, and ethosuximide = 1.29%).

Discussion

Although prescribing AEDs to nonepileptic psychiatric patient populations has become more common, there were previously no reports describing the clinical impact. After analysis of a large sample size of 76 cases, we found that the introduction of AEDs demonstrates a significant improvement on symptom reduction according to the clinic's psychiatrist. In fact, 85.53% of the cases showed a certain degree of symptom improvement. In addition, these results show that utilizing the EEG in order to identify brain abnormalities such as IEDs provides beneficial information.

Although EEG is a noninvasive and widely available tool, this RDoC recommended technology is underutilized in psychiatry. We are not suggesting that EEG be solely used for diagnosis and medication selection purposes, but used to augment the intelligence of the psychiatrist. In using the EEG for these 76 cases, the clinic's psychiatrist was able to gain valuable information about each patient that could not have been derived from a symptoms-based approach alone. These data show that with patients who have IEDs, AEDs may be necessary for symptom improvement.

Another important discussion point of this study is the idea that the AEDs prescribed to these patients were used to stabilize the abnormal activity and in doing so, it made it possible to treat the underlying disorder. This means that the AEDs were assisting the medications targeting specific problems. Many medications lower seizure threshold and increase IED activity. The increased prevalence of IEDs may underlie medication failure in these patients. In several cases where AEDs were added, significant symptoms change were not seen until additional medications were added. For example, after oxcarbazepine stabilized a patient's brain, methylphenidate was added and the ADHD symptoms were resolved. Another example is when a patient was taking lisdexamfetamine before the EEG recording and reported having less severe symptoms after

combining it with lamotrigine. Other examples of positive responses were when patients mentioned experiencing improvement in sleep, positive effects on irritability, less anger, better self-control, more flexibility, and improved social skills. There have even been cases where patients reported worsening of symptoms after stopping the anticonvulsant. One example is when a mother reported her son was acting more aggressive after stopping oxcarbazepine and wanted to put him back on the medication.

Although the results show that the majority of the patients improved, a few patients did not have favorable reactions to the introduction of AEDs. For example, one patient developed Steven-Johnsons syndrome and had to stop taking the AED due to a body rash, while others complained that lamotrigine made them dizzy or gave them headaches. Six of the patients also seemed to have no reaction in relation to their symptoms with the addition of AEDs.

Within our case series, a few notable limitations are present. First, it should be noted that this study was observational in nature and included neither systematic intake and outtake assessments nor a control group. Instead, the study is presented as a retrospective analysis, due to the fact that we were unable to standardize the psychiatrist's chart responses for defining the patient's symptoms. Because of this, only the psychiatrist's subjective impression was used. In the future, we would like to generate an improved evaluation process. Another limitation is due to the fact that we picked these cases retrospectively based solely on the existence of IEDs, no association can be made in respect to their diagnoses. Finally, we would like to disclose that our patient population is derived from a high socioeconomic class due to not accepting insurance. Therefore, the findings cannot be generalized to other socioeconomic classes.

With the completion of this case series study there are a few issues to consider for future research. First, randomized controlled studies are needed in which pre- and post-EEGs have standardized questionnaires comparing levels of impairment and symptoms change. Second, future studies should look into specific AEDs and note those cases where certain AEDs should be selected over others. The effectiveness of particular AEDs may vary according to age, gender, or symptoms. This study had a large age range as well as a very high percentage of males versus females. Varying age and gender in future studies should produce results that would be both interesting and increase our understanding of the relationship between IEDs and AEDs in nonepileptics.

To conclude, 76 nonepileptic patients with IEDs were analyzed after administering AEDs to assess symptoms change. In these refractory patients 85.53% were found to improve after treatment. These preliminary findings suggest that the presence of IEDs may indicate a more positive treatment outcome to anticonvulsant medication. Nevertheless, utilizing EEG to reveal the presence of IEDs is a step toward evidence-based medicine. These results serve as the first retrospective study in which nonepileptic patients with IEDs were treated with anticonvulsants. Our findings also suggest that EEG screening should be considered in patients that have had adverse reactions to psychiatric medications as well as refractory cases regardless of age, gender, or diagnosis.

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Author Contributions

RS, JT, MP, AR, EM, and GK substantially contributed to the conception or design of the paper and contributed to acquisition, analysis, or interpretation of data; RS, AR and EM drafted the manuscript; RS, JT, MP, AR, EM, and GK critically revised the manuscript for important intellectual content; RS, JT, MP, AR, EM, and GK gave final approval and agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Conflicting Interests

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