Original Article

Newer Antiepileptic Drugs Discontinuation due to Adverse Effects: An Observational Study

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Abstract

Aims: Antiepileptic drugs are the main therapy for epilepsy. However, the incidence of adverse effects (AEs) results in treatment discontinuation. The aim of this study is evaluating the factors involved in discontinuation of antiepileptic drugs. **Settings and Design:** We studied 2797 epileptic patients who consumed levetiracetam (LEV), oxcarbazepine (OXC), topiramate (TPM), zonisamide (ZNS), rufinamide, and lacosamide to evaluate the discontinuation because of AEs. **Statistical Analysis Used:** Data were analyzed using descriptive statistics and Chi-square test. **Results:** This study showed the rate of discontinuation due to adverse reactions as follows: TPM (7.10%), OXC (4.5%), ZNS (1.8%), and LEV (1.6%) (Chi-square analysis, $P < 0.0001$). Our study also showed that 1.35% of the patients did not continue the therapy because of subjective experiences of the AEs. Furthermore, neurologic complications in TPM, skin rashes in OXC, and patients' subjective experiences in LEV prescription were the main reasons for nonadherence due to a AEs. **Conclusions:** AEs in newer antiepileptic drugs are extremely prevalent. Our observation revealed that skin rashes and paresthesia were the most probable causes of treatment discontinuation because of AEs.

Keywords: Adverse effects, anticonvulsant, epilepsy, medication adherence

Introduction

Epilepsy with a prevalence rate of 8/1000 is one of the most common chronic neurological disorders.[1] Antiepileptic drugs (AEDs) are often presumed as the choice of treatment in epileptic patients; however, the treatment failure with AEDs is a permanent challenge for the physicians.[2] Adverse effects (AEs) remain an important cause of nonadherence to AEDs in patients with epilepsy.[3] Any AE associated with the therapeutic use of a specific drug in humans is usually considered as a definition of an "AE."[4] In recent decades, new AEDs have been introduced to address the needs of patients with refractory epilepsy or those suffering from AEs of the older drugs; however, even these new medications are not without AEs.

Newer AEDs have a variety of AEs from mild to life-threatening, and many studies have compared AEDs based on their psychiatric, central nervous system (CNS), or general medical AEs. However, there is a controversy in the determination of AEs which are responsible for treatment discontinuation. Although most of the studies consider CNS-related AEs as the main AEs in topiramate (TPM), oxcarbazepine (OXC), and zonisamide (ZNS) consumption.[5-7]

Many studies have focused on the medical aspects of nonadherence to AEDs such as age. Age and sex of patients with epilepsy seem to be relevant to the incidence of adverse experiences.[8,9] Furthermore, noncompliance tends to be higher with a history of psychiatric disorders.[10] However, there is a hypothesis which focuses on patient's health beliefs as a main cause of noncompliance. For instance, patients may stop consuming an AED just because of testing their dependence on epilepsy.[11] However, there are not enough data on newer AEDs. Therefore, we investigated AEDs for rate and reasons of discontinuation.

Subjects and Methods

Data from January 2002 to November 2017 were obtained from Shahid Beheshti University of Medical Sciences database. This database includes medical records of neurologic patients referred to some neurologic clinics of Shahid Beheshti University of Medical Sciences.

The database was run from January 1, 2002, at Loghman Hakim Hospital in Tehran, Iran. Variables included gender, age, brief medical and drug history, the diagnosis, laboratory results, imaging results, the drug prescription, the indication of drug selection, course of treatments, nonadherence to the treatment, and the reason of discontinuation. The study protocol has been approved by the Loghman Hakim Committee on human research.

In this study, epileptic patients receiving at least one new AED were included in the study. New AEDs are drugs which were

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marketed after 1992 such as felbamate, levetiracetam (LEV), rufinamide (RUF), tiagabine, TPM, vigabatrin, and ZNS and lacosamide (LCM). However, felbamate, tiagabine, and vigabatrin are not prescribed in our clinics.

We collected demographic characteristics, AEs and discontinuation reasons for LEV, TPM, ZNS, OXC, RUF, and LCM from the database. In our clinic, "discontinuation" was defined as cessation of specific drug therapy by the physician (with medical indication) or patient's self-report of reluctance to continue drug consumption.[12]

In the current study, we focused on discontinuation due to AEs (DAEs) and excluded other reasons for discontinuation such as price, drug interaction, and poor response to therapy. We also excluded data of drug refractory patients. If an AE has been solved following dose changing, we also did not count it as a DAE. The drug withdrawal was gradual, and the time for withdrawing a drug was from 1 to several weeks (based on symptoms severity). It was because of the severity of AEs.

Here, we report rates and etiologies of discontinuation. In addition, we introduced a category named discontinuation because of a subjective experience of an AE (DSAE). It included a variety of nonspecific complaints which physicians did not consider them as a reason to change in the therapy, but patients insisted on discontinuation.

Descriptive statistics were calculated to describe the patients' characteristics and DAEs for the entire sample. In addition, the Chi-square test was conducted to evaluate the association of variables.

Results

A total of 2797 patients received new antiepileptic drugs. Of these patients, 47% were female. Patient's demographic data are presented in Table 1. Overall, 110 patients experienced AEs which led them to discontinue the treatment (3.9% of all epileptic patients). Some of the patients were admitted to the hospital due to severe symptoms such as TEN and/or Stevens–Johnson syndrome; however, there was not any mortality report among our patients. In our clinics, LEV was the most prescribed newer AED (1092 patients) followed by OXC (981 patient).

Our data revealed discontinuation rates as follows: TPM (7.10%), OXC (4.5%), ZNS (1.8%), and LEV (1.6%). In addition, RUF is just being consumed by one patient and not yet discontinued; also there was no report of discontinuation in five persons who are consuming LCM. Chi-square test confirmed the relation of AEs and AED consumption ($P < 0.0001$).

According to our data, neurologic complaints, such as paresthesia, were the most important reason for DAE (53% of all DAEs). In addition, our study showed 1.35% of the patients could not continue the therapy because of DSAE. In addition, this study disclosed 34% of discontinuations were DSAEs. The third DAE reason was dermatologic problems such as skin rashes [Table 2].

The main reasons for nonadherence to TPM were paresthesia (83%) and nephrolithiasis (4%). Medical causes of OXC nonadherence were dermatologic disorders (50%) and thrombocytopenia (2%). DSAE was leading cause of LEV discontinuation followed by visual hallucination (6%) and dermatologic complaints (6%).

Results of this study also showed 96% of dermatological DAEs in newer antiepileptic drugs were because of OCX, and all of gastrointestinal and metabolic DAEs were because of TPM. However, there was no report of cardiopulmonary complication as a reason for DAE in our data [Table 2].

Discussion

In this descriptive survey of epileptic patients (n = 2741), nearly three (9%) AED consumptions were discontinued due to AEs. Of the studied drugs, TPM had the highest AE-related discontinuation rates, while LEV was the best-tolerated drug.

We found that some medical AEs could affect treatment with AEDs. Our observation revealed skin rashes and paresthesia were the most probable causes of discontinuation due to medical AEs. Skin rashes were the most common reason for discontinuing OXC and paresthesia could strongly affect patients who consumed TPM. We observed OXC consumption was mainly influenced by dermatologic complications and DSAEs, while paresthesia chiefly restricts TPM therapy.

Consistent with previous studies, we found dermatologic AEs should be noticed as an etiology of nonadherence in AED therapy.[13] Our results showed OXC was mainly discontinued due to its cutaneous side effects.[14,15]

In addition, we found TPM had the highest risk for neurological DAEs. This is in consensus with the work of Privitera *et al*. which found similar neurological AE rate (approximately 6%) for TPM.[16] However, our discontinuation rate for TPM (7%) was around half the reported rate of 14.3% by Biton *et al*.[17]

Table 1: Demographic characteristics

	Female (%)	10-	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+	Mean
LEV	59	72	215	341	220	93	53	55	31	12	31.0
OXC	24	44	177	292	214	105	84	37	22	6	32.2
TPM	60	35	173	219	141	48	33	7	6	0	27.3
ZNS	60	2	16	15	11	7	3	2	1	0	29.2

Distribution of patients by age and gender. Data of drugs which prescribed for >5 patient were showed. AED=Antiepileptic drug, LEV=Levetiracetam, OXC=Oxcarbazepine, TPM=Topiramate, ZNS=Zonisamide

Table 2: Antiepileptic drugs discontinuation due to adverse effects.

Adverse effects	LEV	TPM	ZNS	OXC
Dermatologic	1	0	0	22
Drop attack	0	0	1	0
Gastritis	0	2	0	0
Hallucination	1	0	0	0
Nephrolithiasis	0	4	0	0
Paresthesia	0	39	0	0
Thrombocytopenia	0	0	0	1
Weight loss	0	2	0	0
DSAE	16	0	0	21
Total	18	47	1	44

AED discontinuation due to adverse effects classified by type of medical problem. Data of drugs which prescribed for >5 patient were showed. Chi-square analysis of contingency disclosed association between AEDs and medical AEs with $P<0.0001$. AED=Antiepileptic drug, LEV=Levetiracetam, OXC=Oxcarbazepine, TPM=Topiramate, ZNS=Zonisamide, DSAE=Discontinuation because of a subjective experience of an adverse effect. All the included numbers are persons who discontinued the treatment

Giussani *et al*. in 2017 reported that the overall discontinuation rate for adverse events was around 6% for these drugs (compared to our 4%). Furthermore, DAE rates differed for LEV (our 1.6% compared to 5.4%); however, in consensus with our study, TPM was the leading cause of DAE (our 7.1% compared to 9.8%). In addition, we had similar discontinuation rates for OXC (our 4.5% compared to 4.8%).[18] These difference might be justified by larger study population in this study and variations in hepatic enzymes in different races.[19,20]

This study also introduced DSAE as a major cause of DAE (responsible for 33% of discontinuations). Besides, it seems patients who were treated with LEV were chiefly reluctant to continuing the treatment not because of a specific medical side effect but due to DSAEs.

Although there are very few such categorizations in the literature regarding AEDs, there are emerging data that subjective experiences of an AE play a major role in the patient's decision to either continue or discontinue their treatment, especially regarding antipsychotics.[21-23] In a study conducted by Uijl *et al*., most of the subjective complaints turned out to be cognitive of nature followed by general CNS problems.[22] This may explain the absence of some CNS-related AEs as the etiology of DAE in the current study contrary to literature.[6,24,25]

Subjective tolerability and its clinical significance is well-known for clinicians but has been largely underappreciated for researchers as they cannot be easily objectified.[21] This suggests that a patient's personal experience and perspective of a drug could meaningfully affect drug adherence; however, this serious influence on the course of therapy is often neglected. Therefore, the role of consultation with psychiatrists and psychologists should be emphasized when physicians challenged by antiepileptic drugs withdrawal.

Although many studies have investigated risk factors for DAEs, not enough work has been conducted on this matter. Further studies are required to evaluate risk factors for DAEs and how to manage them.

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Conflicts of interest

There are no conflicts of interest.

References

1. Kendler KS, Gallagher TJ, Abelson JM, Kessler RC. Lifetime prevalence, demographic risk factors, and diagnostic validity of nonaffective psychosis as assessed in a US community sample. The National Comorbidity Survey. Arch Gen Psychiatry 1996;53:1022-31.
2. Schmidt D, Schachter SC. Drug treatment of epilepsy in adults. BMJ 2014;348:g254.
3. Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. Lancet Neurol 2012;11:792-802.
4. Greenwood RS. Adverse effects of antiepileptic drugs. Epilepsia 2000;41 Suppl 2:S42-52.
5. Cramer JA, Mintzer S, Wheless J, Mattson RH. Adverse effects of antiepileptic drugs: A brief overview of important issues. Expert Rev Neurother 2010;10:885-91.
6. Dolder CR, Nealy KL. The efficacy and safety of newer anticonvulsants in patients with dementia. Drugs Aging 2012;29:627-37.
7. Friis ML, Kristensen O, Boas J, Dalby M, Deth SH, Gram L, *et al*. Therapeutic experiences with 947 epileptic out-patients in oxcarbazepine treatment. Acta Neurol Scand 1993;87:224-7.
8. Blackburn SC, Oliart AD, García Rodríguez LA, Pérez Gutthann S. Antiepileptics and blood dyscrasias: A cohort study. Pharmacotherapy 1998;18:1277-83.
9. Brown WM, Aiken SP. Felbamate: Clinical and molecular aspects of a unique antiepileptic drug. Crit Rev Neurobiol 1998;12:205-22.
10. Haynes RB, Taylor DW, Sackett DL. Compliance in Health Care. The Johns Hopkins University Press;1979.
11. Conrad P. The meaning of medications: Another look at compliance. Soc Sci Med 1985;20:29-37.
12. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 1986;24:67-74.
13. Yang CY, Dao RL, Lee TJ, Lu CW, Yang CH, Hung SI, *et al*. Severe cutaneous adverse reactions to antiepileptic drugs in Asians. Neurology 2011;77:2025-33.
14. Błaszczyk B, Szpringer M, Czuczwar SJ, Lasoń W. Single centre 20 year survey of antiepileptic drug-induced hypersensitivity reactions. Pharmacol Rep 2013;65:399-409.
15. Christe W, Krämer G, Vigonius U, Pohlmann H, Steinhoff BJ, Brodie MJ, *et al*. A double-blind controlled clinical trial: Oxcarbazepine versus sodium valproate in adults with newly diagnosed epilepsy. Epilepsy Res 1997;26:451-60.
16. Privitera MD, Brodie MJ, Mattson RH, Chadwick DW, Neto W, Wang S. Topiramate, carbamazepine and valproate monotherapy: Double-blind comparison in newly diagnosed epilepsy. Acta Neurol Scand 2003;107:165-75.
17. Biton V, Edwards KR, Montouris GD, Sackellares JC, Harden CL, Kamin M, *et al*. Topiramate titration and tolerability. Ann Pharmacother 2001;35:173-9.
18. Giussani G, Bianchi E, Canelli V, Erba G, Franchi C, Nobili A, *et al*. Antiepileptic drug discontinuation by people with epilepsy in the general population. Epilepsia 2017;58:1524-32.
19. Zand N, Tajik N, Moghaddam AS, Milanian I. Genetic polymorphisms of cytochrome P450 enzymes 2C9 and 2C19 in a healthy Iranian population. Clin Exp Pharmacol Physiol 2007;34:102-5.
20. Lai EC, Hsieh CY, Su CC, Yang YH, Huang CW, Lin SJ, *et al*.

Comparative persistence of antiepileptic drugs in patients with epilepsy: A STROBE-compliant retrospective cohort study. Medicine (Baltimore) 2016;95:e4481.
21. Awad AG. Subjective response to neuroleptics in schizophrenia. Schizophr Bull 1993;19:609-18.
22. Uijl SG, Uiterwaal CS, Aldenkamp AP, Carpay JA, Doelman JC, Keizer K, *et al*. A cross-sectional study of subjective complaints in patients with epilepsy who seem to be well-controlled with anti-epileptic drugs. Seizure 2006;15:242-8.
23. Awad AG. Subjective tolerability of antipsychotic medications and the emerging science of subjective tolerability disorders. Expert Rev Pharmacoecon Outcomes Res 2010;10:1-4.
24. Arif H, Buchsbaum R, Pierro J, Whalen M, Sims J, Resor SR Jr., *et al*. Comparative effectiveness of 10 antiepileptic drugs in older adults with epilepsy. Arch Neurol 2010;67:408-15.
25. Marson AG, Kadir ZA, Hutton JL, Chadwick DW. The new antiepileptic drugs: A systematic review of their efficacy and tolerability. Epilepsia 1997;38:859-80.