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Review Article

POTENTIAL PROBLEMS IN GENERIC SUBSTITUTION OF ANTIEPILEPTIC DRUGS: SYSTEMATIC REVIEW

MEILANI[1], BURHANNUDIN ICHSAN[2*]

[1]Postgraduate School, Master of Pharmacy, Universitas Muhammadiyah Surakarta (UMS), Jalan Ahmad Yani, Sukoharjo-57169, Central Java, Indonesia. [2]Faculty of Medicine, Universitas Muhammadiyah Surakarta (UMS), Surakarta, Indonesia
*Corresponding author: Burhannudin Ichsan; *Email: bi268@ums.ac.id

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ABSTRACT

This research aims to identify potential problems arising from substituting generic Antiepileptic Drugs (AEDs). The systematic review utilized databases including PubMed, Science Direct, Google Scholar, ProQuest, and Scopus. Search keywords encompassed (Epilepsy OR "Seizure Disorder" OR Aura) and ("Drug Substitution" OR "Therapeutic Substitutions" OR "Drug Switching" OR "Generic Substitution" OR "Generic Substitutions") and (Brand). The inclusion criteria were all journals related to generic substitution of AEDs, research journals published from May 2015 to March 2022, and potential problems related to the bioequivalence of generic antiepileptic drugs and clinical outcomes therapy in epilepsy patients after generic substitution of antiepileptic drugs. Clinical outcomes can be seizure frequency, Adverse Events (AEs), Quality of Life (QoL), electroencephalogram (EEG) examination, laboratory evaluation, switchback rate, and emergency room visits. A total of 1,010 articles were identified, and 15 full-text articles were included for analysis. Most studies found no significant differences in seizure frequency, AEs, EEG findings, or laboratory results before and after substitution. Moreover, generic substitution did not adversely affect QoL. Although a small percentage of patients reverted to branded drugs, the switchback rate was minimal, and no notable increase in emergency room visits was reported. Overall, the substitution of generic AEDs is clinically safe and effective, with no significant impact on patient outcomes.

Keywords: Generic Substitution, Epilepsy, Seizure Frequency, Adverse Events, Bioequivalence.

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INTRODUCTION

Epilepsy is a brain disorder characterized by abnormal electrical activity resulting in seizures or unusual behavior, sometimes leading to loss of consciousness [1]. Epilepsy is one of the most common neurological disorders, affecting nearly 50 million people of all ages worldwide. Almost 80% of people with epilepsy live in low-and middle-income countries (LMIC). Epilepsy has significant economic implications in terms of healthcare needs [1].

The use of generic drugs, equivalent to branded or reference drugs but cheaper, presents a significant opportunity to reduce healthcare expenditures. The term "Antiepileptic Drugs (AEDs) substitution or switch" generally refers to the practice of changing from one product to another within the same AEDs, whether replacing a branded AEDs with a generic alternative (or vice versa) or switching between generic AEDs products manufactured by different companies [2]. The substantial cost reduction associated with generic AEDs plays a crucial role in patient compliance due to significantly lower prices than branded products [3]. In developed countries, generic drugs account for over 89% of the market. Given that their prices are at least 75% lower than those of brand-name drugs, their availability offers clear economic benefits for patients, the healthcare system, and insurance companies [4]. However, physicians and patients remain cautious about the potential risks of substituting branded AEDs with generics [5]. Issues of bioequivalence and therapeutic equivalence are considered when switching from branded to generic AEDs [6].

A previous systematic review covering literature from 1980 to 2015 concluded that generic AEDs substitution could lead to potential problems related to bioequivalence, drug therapy failure, emergence of Adverse Events (AEs), and increased seizure frequency [7]. Some of these potential problems may cause patients to switchback. This behavior, known as a "generic-to-brand switchback," refers to instances where a patient transitions from a generic drug to its branded drug [8]. Substituting generic drugs in epilepsy patients can pose problems, as the US Food and Drug Administration (FDA) allows too much variability in products. The standard bioequivalence range (80% to 125%) appears too broad for many anti-seizure medications, especially those with narrow therapeutic and toxic levels [6]. Furthermore, concerns regarding bioequivalence criteria for generic drug approval arise because studies demonstrating generic drug bioequivalence are conducted on healthy volunteers with single doses, hence not representing real-world AEDs use [9].

Recent prospective cohort studies indicate that transitioning from brand AEDs to generic drugs is generally safe and does not lead to increased seizure frequency or AEs [5, 10]. Based on these findings, this latest systematic review was conducted to identify potential problems that may arise as a result of switching to generic AEDs, such as the problem of generic drug bioequivalence and the clinical outcomes of epilepsy patients after switching from branded to generic AEDs.

MATERIALS AND METHODS

Inclusion criteria

The inclusion or eligibility criteria for this study were all types of quantitative research, all journals related to the generic substitution of antiepileptic drugs (AEDs), all countries and all races, all ages and all genders, English language journals, research subjects in humans, and potential problems related to the bioequivalence of generic AEDs (the bioequivalence range of 80.00–125.00% with a 90% Confidence Interval (CI)) and clinical outcomes in epilepsy patients after generic substitution of AEDs. Clinical outcomes can be seizure frequency, Adverse Events (AEs), Quality of Life (QoL), electroencephalogram (EEG) examination, laboratory evaluation, switchback rate, and emergency room visits. This study reviewed literature published from May 2015 to March 2022 as an update to the previous review by Atif *et al.* (2016), which covered the period from 1980 to April 2015 [7].

Information sources and search

This study conducted a literature search using five electronic databases: PubMed, ScienceDirect, Google Scholar, ProQuest, and Scopus. Gray literature was excluded from this review, as comprehensive coverage was deemed sufficient through the utilization of these selected databases. The keywords used in the article search are (Epilepsy OR "Seizure Disorder" or Aura) and ("Drug Substitution" or "Therapeutic Substitutions" or "Drug Switching" or "Generic Substitution" or "Generic Substitutions") and (Brand).

Study selection

These keyword combinations are entered into five predetermined databases. The search results from the five databases were then combined into one and filtered. The combined titles of articles obtained as duplicates were then removed. The next stage is screening titles and/or abstracts based on inclusion criteria.

Data collection

Articles that meet the requirements are then collected in the form of a table consisting of author and year, drug studied, study design, research subject, research results, and conclusions.

Analysis

The narrative analysis is used in this systematic review.

RESULTS AND DISCUSSION

Study selection

A total of 1,010 articles were identified through a literature search conducted across five electronic databases, as presented in table 1. After screening for duplication, the number of articles was 712. Screening of titles and/or abstracts based on inclusion criteria resulted in 29 articles. All 29 articles were downloaded. After adjusting to the eligibility criteria, 15 articles were obtained for analysis.

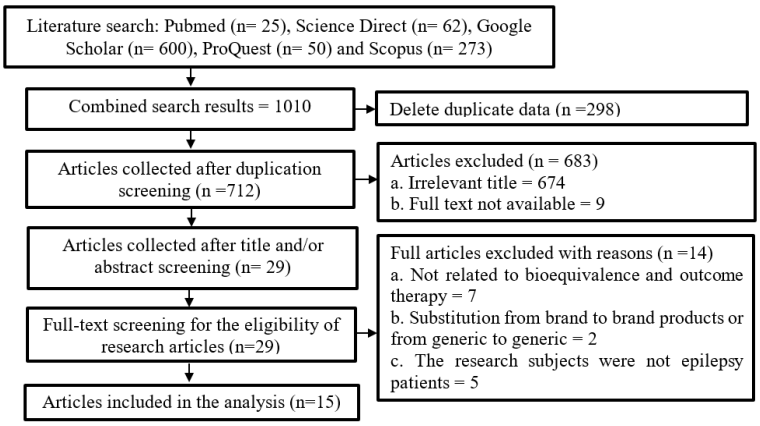

Fig. 1: PRISMA research flow diagram

Study characteristics

The characteristics of the articles analyzed in this systematic review are shown in table 1. The research design that is most often carried out in this systematic review is the cohort design. The Antiepileptic Drugs (AEDs) studied in most of these articles is levetiracetam (LEV). LEV is a relatively new AEDs that has been approved and widely used for the treatment of partial or generalized epilepsy in children and adults [3].

The research articles in this systematic review were conducted on the Asian continent (three articles), Europe (ten articles), and North America (two articles).

Table 1: Characteristics of research articles that meet the eligibility criteria

No	Authors	Study drugs	Design study	Subject (n)
1	Ting *et al.* (2015)	Lamotrigine	Randomized Controlled Trial	34
2	Polard *et al.* (2015)	Carbamazepine, lamotrigine, valproate acid, oxcarbazepine, and topiramate	Case crossover	8.379
3	Bosak *et al.* (2017)	Levetiracetam	Retrospective cohort	159 (8 continued to use branded, 151 switched to generic)
4	Fanella *et al.* (2017)	Levetiracetam	Prospective cohort	36
5	Reimers *et al.* (2017)	Levetiracetam	Prospective cohort	33 (17 continued to use branded, 16 switched to generic)
6	Berg *et al.* (2017)	Lamotrigine	Randomized Controlled Trial	49
7	Markoula *et al.* (2017)	Levetiracetam	Prospective cohort	12
8	Lee and Jung (2018)	Levetiracetam	Retrospective cohort	148
9	Trimboli *et al.* (2018)	Levetiracetam	Prospective cohort	180 (55 continued to use branded, 125 switched to generic)
10	Lang *et al.* (2018)	Valproate, levetiracetam, carbamazepine, and lamotrigine	Retrospective cohort	3530
11	Olsson *et al.* (2019)	Levetiracetam	Prospective cohort	32 (16 continued to use branded, 16 switched to generic)
12	Bosak *et al.* (2019)	Oxcarbazepine	Prospective cohort	103 (27 continued to use the branded, 76 switched to generic)
13	Lang *et al.* (2021)	Valproate, levetiracetam, lamotrigine, sulthiame, and oxcarbazepine	Retrospective cohort	678
14	Tharavichitkun *et al.* (2022)	Levetiracetam	Retrospective cohort	75
15	Tiamkao *et al.* (2022)	Levetiracetam	Prospective cohort	96 (35 continued to use branded, 61 switched to generic)

Risk of bias

This systematic review assessed the risk of bias using the Critical Appraisal Skills Programme (CASP) tools, tailored for both cohort studies [23] and Randomized Controlled Trial (RCT) [24]. The results of the risk of bias assessment for the synthesized cohort studies are presented in table 2.

Table 2: Risk of bias in cohort studies employing the CASP checklist

Author	Item													
	1	2	3	4	5a	5b	6a	6b	7	8	9	10	11	12
Fanella *et al.* (2017)	Yes	Yes	Yes	Yes	Can't Tell	No	Yes	Yes	Yes	Can't Tell	Can't Tell	Yes	Yes	Yes
Bosak *et al.* (2017)	Yes	Yes	Yes	Yes	Ya	Ya	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Reimers *et al.* (2017)	Yes	Yes	Yes	Yes	Ya	Ya	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Markoula *et al.* (2017)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lee and Jung (2018)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Trimboli *et al.* (2018)	Yes	Yes	Yes	Yes	Yes	Can't Tell	Yes	Yes	Yes	Can't Tell	Yes	Yes	Yes	Yes
Lang *et al.* (2018)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't Tell	No	Yes
Olsson *et al.* (2019)	Yes	Yes	Yes	Yes	Can't Tell	No	Yes	Yes	Yes	Can't Tell	Can't Tell	Yes	Yes	Yes
Bosak *et al.* (2019)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't Tell	Yes	Yes	Yes	Yes
Lang *et al.* (2021)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't Tell	Yes	Yes
Tharavichitkun *et al.* (2022)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't Tell	Yes	Yes	Yes
Tiamkao *et al.* (2022)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

The risk of bias analysis conducted on 12 cohort studies revealed that 10 studies demonstrated good quality, as evidenced by most assessment items receiving a "yes" response [3, 5, 10, 13, 15, 17, 18, 20–22]. Conversely, the remaining two studies exhibited lower quality due to "no" and "unclear" responses, particularly concerning the identification and control of confounding factors, which may affect the validity of the study outcomes [14, 19]. Nonetheless, overall, the studies included in this systematic review are considered to possess acceptable quality.

Table 3: Risk of bias in RCT studies employing the CASP checklist

Author	Item												
	1	2	3	4a	4b	4c	5	6	7	8	9	10	11
Ting *et al.* (2015)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Berg *et al.* (2017)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

The risk of bias assessment for both RCT indicated generally good methodological quality, as all critical appraisal items were answered with "yes" [11, 16]. This suggests that the studies had a low risk of bias. Studies with a low risk of bias are less likely to produce distorted findings, thereby improving the accuracy and reliability of the systematic review results. The results of the risk of bias assessment in the RCT study can be seen in table 3.

Bioequivalence

The articles in this systematic review conducted the generic drugs bioequivalence test on epilepsy patients who underwent generic substitution as shown in table 4. Bioequivalence (BE) is assessed using two pharmacokinetic parameters: the maximum plasma concentration (Cmax) and the area under the plasma concentration-time curve (AUC), which reflect the rate and extent of drug absorption. Based on BE standards, differences in Cmax and AUC between a generic drug and its reference counterpart are acceptable within a range of-20% to+25%. According to the US Food and Drug Administration (FDA), the bioequivalence criteria are 80.00–125.00% with a 90% confidence interval (CI) [25]. Bioequivalence studies are generally performed to confirm that a generic drug exhibits similar pharmacokinetic and pharmacodynamic characteristics to its branded drugs [26].

Table 4 shows that generic drugs are bioequivalent to branded drugs because they meet the acceptance interval of 80-125% with a 90% confidence interval (CI) [11, 14–17]. The concern in this study is that the measurement of bioequivalence for generic drugs was conducted on lamotrigine and levetiracetam, which have a wider therapeutic index.

The therapeutic index is a crucial parameter in pharmacology, reflecting the safety margin of a drug. Drugs with a wider therapeutic index, such as levetiracetam and lamotrigine, offer a broader safety margin, making generic substitution safer even if there are small variations in generic plasma drug concentrations. This is in contrast to drugs with a Narrow Therapeutic Index (NTI), which have a slim margin between efficacy and toxicity, such as phenytoin and carbamazepine [27]. NTI drugs, also known as 'critical dose drugs', are sensitive to small variations in plasma concentrations, which can lead to inadequate therapeutic responses or the emergence of side effects. Therefore, the acceptance range for bioequivalence in NTI drugs is tightened to 90–111%, compared to the standard 80–125% [25].

Table 4: Bioequivalence of generic AEDs in epilepsy patients

No	Authors	Result	Conclusion
1	Ting *et al.* (2015)	The average steady-state AUC is 97.2–101.6%, Cmax is 98.8–104.5% at 90% CI	Generic products are bioequivalent to branded products
2	Markoula *et al.* (2017)	The average AUC ratio is 100.4–119.1%, and Cmax is 99.3–119.5% at a 90% CI	Generic products are bioequivalent to branded products
3	Fanella *et al.* (2017)	The average serum concentration drug before switching was 22.47 mcg, while after switching to generic, it was 23.29 mcg, with a P value = 0.5 using the Wilcoxon test statistics	There was no significant difference in the variability of serum concentrations in patients before and after switching to generics
4	Reimers *et al.* (2017)	The ratio of the mean serum concentration drug to the normalized dose (1500 mg) and the 90% confidence interval indicates a range of values of 80–125%	Generic products are bioequivalent to branded products
5	Berg *et al.* (2017)	Average AUC is 96.29–101.9%, Cmax is 92.6–110.4%, and Cmin is 93.4–101.0% at 90% CI	Generic products are bioequivalent to branded products

AUC: area under the plasma concentration, Cmax: maximum plasma concentration, CI: confidence interval

Nonetheless, this rule is still insufficient to ensure the safety and effectiveness of treatment in some cases, for example, in patients with high interindividual variability (such as elderly patients or those with comorbidities), there is a higher risk of treatment complications [25]. Several pharmacological factors that increase the risk of treatment complications because of drug use in the elderly include changes in body composition and serum albumin levels, total body water, as well as liver and kidney function [28]. As a result, substituting NTI drugs may pose dangers to patients. Because of the narrow margin between safe and toxic doses, some experts have expressed concerns about the therapeutic equivalence of generics for these drugs and have proposed not allowing generic substitution for NTI drugs [25].

Based on the results of this study, it can be concluded that the incidence of recurrent seizures and adverse events that can occur in patients who use generic substitution of AEDs may not be caused by the bioequivalence effect of the generic products, especially in AEDs with a wider therapeutic index.

Seizure frequency

Seizure frequency was determined based on the number of seizures observed while the patient was using the branded drug (before substitution) and while switching to the generic drug (after substitution). Table 5 shows the frequency of seizures in patients before and after generic substitution. Eight articles report no significant differences in seizure frequency following substitution [3, 5, 10, 13, 14, 17, 20, 21]. One article showed that the group receiving generic substitution experienced significantly better seizure control [22], while another reported a significant increase in seizure risk after substitution [18]. In general, the substitution of AEDs does not appear to affect seizure frequency.

Studies conducted by Lang *et al.* (2018; 2021) in Germany utilized the same database, namely the IMS® Disease Analyzer (IQVIA, Frankfurt, Germany), as well as a similar study design (retrospective cohort) and identical case-control selection criteria. Nevertheless, the two studies produced conflicting findings. The 2021 study, which focused on a pediatric and adolescent population (<18 y), concluded that generic substitution was not associated with an increased risk of seizure recurrence. In contrast, the 2018 study found that, in adults, generic substitution was linked to a higher incidence of recurrent seizures [18, 20].

These divergent results may be attributed to differences in patient adherence to treatment. In the 2018 study, approximately 40% of participants were over the age of 60, a group generally at higher risk of non-adherence, particularly when confronted with changes in the shape, color, or packaging of generic medications. Such changes are known to trigger nocebo effects and are considered independent risk factors for non-adherence in the elderly, although this was not explicitly measured in the study. Meanwhile, in the 2021 study, adherence was likely higher, as medication use in children is typically supervised directly by parents, an aspect that may have contributed to the absence of increased seizure recurrence following generic substitution [18, 20].

Previous studies have shown clinical risks associated with switching from branded to generic AEDs, for example, associated with increased seizure frequency, increased toxicity, and increased emergency room visits [12, 29-31]. The increased frequency of seizures may occur in some patients who take AEDs every day, this may be called a seizure cluster. Some people with epilepsy may experience seizure clusters (acute repetitive seizures, serial seizures), which are acute episodes of increased repetitive seizures that differ from the person's usual seizure pattern. Seizure clusters are unpredictable. Risk factors for seizure clusters include high seizure frequency, history of status epilepticus, and drug-resistant epilepsy [32]. In addition, some additional psychological aspects related to the process of switching from branded to generic AEDs may contribute to increased seizure frequency in a small proportion of patients. These psychological factors may appear as patient anxiety when encountering medication that looks different from what they are accustomed to taking [12].

According to the American Epilepsy Society (AES), the occurrence of problems after switching to generic AEDs, such as an increase in seizure frequency, duration, or severity, may lead patients to attribute these changes to the substitution, even though natural variations in seizures could be the actual cause. Other reasons, such as emotional stress from switching or decreased compliance due to differences in pill appearance, may lead to seizures or side effects [33]. Compliance with treatment is crucial, as it directly influences therapy outcomes. Non-compliance to follow prescribed therapy can lead to negative consequences, including treatment failure and higher hospitalization rates [34]. Counseling and providing education may improve adherence [35]. Enhancing adherence is not solely the patient's responsibility; it also requires effective collaboration among the government, healthcare professionals, the community, and the patient's family to achieve therapeutic goals [36].

Table 5: Comparison of seizure frequency after generic AEDs substitution

S. No.	Authors	Results	Conclusion	Statistic test
1	Fanella *et al.* (2017)	There are 33 patients who did not experience seizures before or after the generic substitution	There was no difference in seizure frequency before and after generic substitution	No statistical tests
2	Markoula *et al.* (2017)	The average frequency of seizures before substitution was 1.2, and after generic substitution was 1.3	There was no significant difference in seizure frequency between patients before and after generic substitution	No statistical tests
3	Bosak *et al.* (2017)	An increase in seizure frequency only occurred in 9 patients (6%) of 151 patients who underwent generic substitution; 8 patients who continued to use branded drugs did not show an increase in seizure frequency	The increase in seizures after generic substitution is minimal	No statistical tests
4	Trimboli *et al.* (2018)	The average frequency of seizures in patients before substitution was 2.4 with 95% CI, and after generic substitution, it was 2.3 with 95% CI, P value = 0.71	There was no statistically significant difference in seizure frequency after substitution of generic AEDs	Wilcoxon signed-rank test[a]
5	Lee and Jung (2018)	The difference in seizure frequency before and after generic substitution has a P value of 0.886	There was no statistically significant difference in seizure frequency after the generic substitution of AEDs	Wilcoxon signed-rank test[a]
6	Lang *et al.* (2018)	The risk of recurrent seizures after switching to a generic product has OR = 1.85, 95% CI 1.30-2.64, with a P value<0.001	Generic substitution of AEDs increases the risk of seizures 1.85 times and is statistically significant	Multivariate logistic regression test[b]
7	Bosak *et al.* (2019)	The mean frequency of seizures (±SD) in patients before substitution was 4.6±8.1 and after generic substitution was 4.9±9.9 with a P value = 0.600	There was no statistically significant difference in seizure frequency after the generic substitution of AEDs	Wilcoxon signed-rank test[a]
8	Lang *et al.* (2021)	The risk of recurrent seizures in epilepsy patients after generic substitution has an OR = 0.56, 95% CI 0.23-1.37	Generic substitution of AEDs does not cause the risk of recurrent seizures	Multivariate logistic regression test[b]
9	Tharavichitkun *et al.* (2022)	The mean seizure frequency (±SD) before and after generic substitution was 2.77 ±11.41 and 3.15 ±14.47 respectively with P value=0.907	There was no statistically significant difference in seizure frequency after substitution of generic AEDs	Wilcoxon signed-rank test[a]
10	Tiamkao *et al.* (2022)	There were 91.80% of patients who experienced seizure control after generic substitution, and 45.71% of patients who remained on branded drugs experienced seizure control after the transition period, with a P value<0.0001	There was a statistically significant difference regarding seizure control in the two groups. The group with generic substitution had significantly higher seizure control	Logistic regression analysis[b]

AEDs: Antiepileptic Drugs, CI: Confidence Interval, OR: Odds Ratio, SD: Standard Deviation, Note: [a]non-parametric data, [b]parametric data

Adverse events (AEs)

Adverse Events (AEs) are injuries or any unintentional harm that occur during medical care, which are significant to a greater extent than the underlying pathology. They can occur during prolonged hospitalization or delayed discharge, and lead to health detriment, disability, or even patients' death [37].

Table 6 shows a comparison of AEs in patients who underwent generic substitution of AEDs. Four articles compare the AEs that occurred in one group of patients before and after generic substitution, where two articles conducted statistical tests while the other two articles did not conduct statistical tests [5,14,17,19]. However, in general, the results of the analysis showed that there were no significant differences in AEs in patients after generic substitution of AEDs, and AEs occurred only in a minimal percentage of patients.

Three other articles compare AEs in patients who made a generic substitution and those who remained on the branded drug after the specified switch date [10, 13, 22]. Two articles conducted statistical tests [10, 22], while one article did not conduct statistical tests [13]. The results of the analysis showed that there were no differences in AEs in the two groups.

In this analysis, there are limitations because there is only one article available, which is the research article by Bosak *et al.* (2017). The research compared AEs that occurred in 151 patients who switched to generics with 8 patients remaining on branded-name drugs after the specified switch date. Because of this, it is difficult to draw definitive conclusions due to the significant difference in patient numbers. However, in patients who underwent generic substitution of AEDs, AEs only occurred in a minimal percentage of patients, which is 4% (table 6) [13].

In this study, AEs related to levetiracetam were the most frequently investigated. AEs can be divided into mild, where patients continue using the generic drug because all side effects were resolved by the second follow-up visit and did not lead to any modification in treatment, and severe, where patients discontinued treatment or returned to using the branded drug. Mild AEs reported include heartburn [5], mild allergic reactions [5], headache [5, 14], somnolence [13], dizziness [10, 13], abdominal discomfort [5, 10], and mild irritability [13]. Severe AEs included burning sensation [5], diarrhea [5], panic attacks [5], irritability [5, 14], depression, and mood changes [14].

This is supported by previous studies showing that AEs that may occur during levetiracetam treatment include somnolence, dizziness, anorexia, fatigue, headache, sedation, and irritability. The most common were somnolence, fatigue, and dizziness, which gradually disappeared and did not require discontinuation of levetiracetam [38].

Other studies have shown that levetiracetam can also cause psychiatric symptoms in patients with epilepsy. Most of the psychiatric symptoms caused by the drug are mild, short-lived, and significantly improve or resolve with long-term use without serious consequences. Hallucinations, delusions, irritability, aggressive behavior, and self-harming or violent actions are the prominent clinical manifestations. Severe psychiatric symptoms often do not resolve on their own; in such cases, dose reduction, discontinuation of the drug, or even the addition of antipsychotic medications may be necessary to manage the patient [39]. AEDs are also known to be one of the causes of Stevens-Johnson Syndrome (SJS). The risk of SJS is higher with the use of phenytoin and carbamazepine compared to sodium valproate and levetiracetam, with levetiracetam being the safest option [40].

The increased incidence of AEs observed in patients undergoing substitution from branded to generic AEDs cannot be attributed solely to differences in bioequivalence. Psychological factors, such as anxiety triggered by changes in the physical appearance of the medication, and reduced treatment adherence, also play a substantial role in the manifestation of these side effects. Alterations in the shape, color, or packaging of generic formulations may induce uncertainty or discomfort in patients, potentially affecting their perception of the drug's efficacy and safety. Such perceptions can undermine adherence to the prescribed regimen, thereby increasing the risk of AEs or seizure recurrence. To minimize the negative impact of these factors, providing medication counseling during the substitution process is an essential step [33].

Based on this analysis shows that the substitution of generic AEDs occurred in only a small number of patients and did not result in an increase in AEs in epilepsy patients after the generic substitution. Therefore, switching from branded to generic AEDs is generally safe for epilepsy patients.

Table 6: Comparison of AEs in epilepsy patients who undergo generic substitution for antiepileptic drugs

No	Authors	Results	Conclusion	Statistic test
1	Markoula *et al.* (2017)	The average AEs±SD score before generic substitution was 33.6±14.2 while after generic substitution it was 33.8±10.2 with a P value = 0.95	There was no statistically significant difference in AEs in patients after the generic substitution of AEDs	T-test[a]
2	Bosak *et al.* (2017)	Of the 151 patients who made the generic substitution, only 6 patients (4%) experienced AEs, while the 8 patients who continued to use branded AEDs after the switching date did not show any AEs	Definitive conclusions cannot be drawn from this study because of the significant difference in the number of patients, but AEs only occur in a minimal percentage	No statistical analysis
3	Fanella *et al.* (2017)	There were 3 patients (8%) of 36 patients who experienced AEs after generic substitution	In general, AEs only occur in a minimal percentage of patients after generic substitution	No statistical analysis
4	Trimboli *et al.* (2018)	There are 31 patients (25%) who experienced AEs before generic substitution and 30 patients (24%) who experienced AEs after generic substitution, with P value = 0.86	There was no statistically significant difference in AEs in patients after the generic substitution of AEDs	Mann–Whitney U test[b]
5	Bosak *et al.* (2019)	There is 1 patient (3.7%) who continued to use branded AEDs after switching and experienced an AEs, while 4 patients (5.3%) who made a generic substitution experienced an AEs, with a P value = 0.75	There was no statistically significant difference in AEs between the branded groups and the generic groups	Mann–Whitney U test[b]
6	Olsson *et al.* (2019)	There are 2 patients before the generic substitution experienced AEs, but after the substitution, experienced AEs improvement in symptoms	In general, AEs only occur in a minimal percentage of patients with generic substitution	No statistical analysis
7	Tiamkao *et al.* (2022)	There is 1 patient (1.64%) in the generic group experienced an AEs after substitution while in the branded group experienced an AEs, namely 1 patient (2.86%) with a P value = 0.999	There was no significant difference in AEs in the generic group and branded group	Logistic Regression Analysis[c]

AEs: Adverse Events, SD: Standard Deviation, AEDs: Antiepileptic Drugs, Note: [a]Parametric data, [b]Non-parametric data, [c]Parametric data

Quality of life (QoL)

Improving Quality of Life (QoL) is one of the most important goals in epilepsy treatment [19]. People with epilepsy have a lower QoL than healthy individuals and individuals with other chronic diseases. Therefore, improving QoL for people with epilepsy is a major clinical priority [41]. Table 7 shows the QoL of patients after the generic substitution of AEDs.

QoL assessments used the Quality of Life in Epilepsy (QOLIE)-31s questionnaire. The QOLIE-31 is a validated and frequently used epilepsy-specific instrument, designed for the assessment of health-related QoL in people with epilepsy. This instrument contains 31 items, grouped into seven subscales, namely seizure concerns, overall QoL, emotional well-being, energy/fatigue, cognitive function, medication effects, and social function. In addition, an overall score was taken by calculating the weighted average of the subscales according to manual scoring. Scores can range from 0 to 100, with higher scores indicating better QoL [19].

In the study conducted by Olsson *et al.* (2019), using the QOLIE-31 instrument, the overall QoL subscale scores were similar before and after substitution, suggesting that generic substitution did not lead to a decline in patients' QoL. The subscales that showed significant improvement were seizure worry and social functioning scores. An increase in the seizure worry score implies reduced concern about seizures. This may be due to more frequent contact with epilepsy nurses, which made patients feel safer and more comfortable. Extra monitoring is a natural part of most prospective studies and may help counteract the nocebo effect and contribute to lower switchback rates [19].

This study has several limitations that warrant consideration when interpreting the findings. The use of a non-randomized, open-label design may have introduced selection bias, as potential confounding factors, such as epilepsy severity, socioeconomic status, or educational level, were not explicitly controlled. Nonetheless, no significant differences were identified between groups in key variables potentially influencing QoL, including seizure burden and the number of AEDs [19].

Based on both articles, the substitution of generic AEDs does not have a negative impact on the QoL of epilepsy patients, indicating that generic substitution can be safely carried out. Improving QoL is essential in demonstrating the success of therapy and can be achieved through pharmaceutical care, which entails providing direct and responsible services to patients related to pharmaceutical preparations, aiming for specific outcomes that enhance their well-being [42].

Table 7: Description of the results of assessing the QoL of epilepsy patients using the QOLIE-31 questionnaire after generic substitution

No	Authors	Conclusion
1	Fanella *et al.* (2017)	Quality of life assessment based on QOLIE-31 showed global improvement after switching to generics
2	Olsson *et al.* (2019)	Quality of life assessment based on QOLIE-31 showed improvement after switching to generics

QOLIE: Quality of life assessments used the Quality of Life in Epilepsy

Electroencephalogram (EEG) and laboratory evaluation

One of the important examinations in epilepsy patients is the Electroencephalogram (EEG). Apart from confirming the diagnosis of epilepsy, an EEG examination can also be carried out to monitor the response to AEDs therapy [43]. In addition to neurological examination, laboratory evaluation can be used as an additional test for examination in patients with epilepsy. Examination of leukocyte (WBC) levels, erythrocyte (RBC) levels, hemoglobin, hematocrit, creatinine kinase, and ammonia was significantly associated with epileptic seizures. However, serum ammonia levels are the most relevant laboratory test for predicting epileptic seizures. The increase in oxygen demand during seizures can lead to the release of lactate, ammonia, and creatine kinase from the damaged tissues and skeletal muscles [44]. The results of EEG examinations and laboratory evaluations in patients after generic substitution can be seen in table 8.

Table 8 shows that the study by Trimboli *et al.* (2018), who conducted EEG examinations on 125 patients before and after generic substitution for levetiracetam, showed that the EEG findings did not change when the patient was still using the branded or after the patient used the generic drug AEDs [5]. Table 8 also shows the laboratory tests performed by Tiamkao *et al.* (2022). The laboratory test was conducted on 61 patients who underwent generic LEV substitution and then compared them with 35 patients who continued to use branded LEV. From the results of this study, it was found that in patients who used generic LEV, no laboratory abnormalities were found, while the 2 patients who continued to use branded LEV showed laboratory examination abnormalities. After carrying out statistical tests, it was found that there were no significant differences between the two groups, but the limitation of the article is that it does not mention what laboratory tests were carried out [22].

Switchback rate

"Switchback" is defined as a patient switching from a branded drug to a generic drug and then switching back to a branded drug [8]. The switchback rate is the percentage of patients who switch back to branded drugs after previously using generic substitutions. The transition rate can be seen in table 9.

Table 8: EEG results and laboratory evaluation in epilepsy patients

No	Authors	Conclusion
1	Trimboli *et al.* (2018)	EEG findings did not change before or after generic substitution
2	Tiamkao *et al.* (2022)	There was no statistically significant difference regarding laboratory abnormalities in the group of patients who made generic substitutions and patients who continued to use branded drugs with a P value = 0.130

EEG: Electroencephalogram

Table 9: Switchback rates of epilepsy patients after generic substitution

No	Authors	Results
1	Fanella *et al.* (2017)	The switchback rate was 8%.
2	Bosak *et al.* (2017)	The switchback rate was 1.3%
3	Olsson *et al.* (2019)	No switchback occurs (0%)
4	Tharavichitkun *et al.* (2022)	The switchback rate due to recurrent seizures is 5.5%, while the return rate due to AEs is 1.3%
5	Tiamkao *et al.* (2022)	No switchback occurs (0%)

AEs: Adverse events

The causes of the transition back are the occurrence of repeated seizures [13, 21] and the occurrence of adverse events [14, 21]. Based on table 9, five articles show the conversion rate of epilepsy patients after generic substitution. Research by Tiamkao *et al.* (2022) and Reimers *et al.* (2017) showed that patients who underwent generic substitution did not make a switchback [15, 22]. This could be because generic drugs have a much higher level of seizure control than branded drugs, and the AEs that occur are not significantly different between generic and branded drugs [22]. Another study conducted by Olsson *et al.* (2019) also showed that there was no switchback in patients who had used the branded which could be due to reduced seizure anxiety in patients who had switched to generic drugs which could be seen from the increase in scores on the QOLIE subscale after generic substitution [19].

Emergency room visit

The unexpected occurrence of recurrent seizures often results in outpatient visits, emergency room evaluations, and/or hospitalization to adjust and treat injuries related to the effects of generic substitution of AEDs [2]. Table 10 shows that emergency room visits occurred after the generic substitution of AEDs [12, 22]. Based on these two articles, it shows that emergency room visits in patients after generic substitution of AEDs do not significantly occur, and generic substitution is not related to the level of hospitalization in epilepsy patients.

Table 10: Comparison of emergency room visits in epilepsy patients

No	Author	Results	Conclusion	Statistic test
1	Tiamkao *et al.* (2022)	Patients with generic LEV who visited the emergency room during the study period were 2 patients (3.28%), while patients who continued to use the branded were 4 patients (11.43%), with a P value = 0.186	There was no statistically significant difference in emergency room visits between the two groups after the switch to generics	Logistic regression analysis
2	Polard *et al.* (2015)	Emergency room visits in patients with epilepsy had an OR of 0.97 (95% CI: 0.86–1.10), with a P value = 0.42	There were no statistically significant differences in emergency room visits after the generic switching of antiepileptic drugs	Logistic regression analysis

LEV: Levetiracetam, OR: Odds Ratio

CONCLUSION

Generic substitution of AEDs is a clinically viable and cost-effective approach to epilepsy management. This review found no significant differences in seizure frequency, adverse events, EEG findings, or laboratory results between generic and branded formulations. Moreover, patients' quality of life (QoL) either improved or remained stable after substitution. While a small proportion of patients reverted to branded drugs, the switchback rate was low and not linked to increased emergency care visits. However, as most available evidence centers on levetiracetam, an AEDs with a relatively broad therapeutic index, the findings may not be fully generalizable to drugs with narrower therapeutic windows. Therefore, pharmacist-led counseling during the substitution process is vital to reinforce patient confidence, reduce nocebo effects, and improve treatment adherence.

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AUTHORS CONTRIBUTIONS

Conceptualization: BI, M; methodology: BI, M; data curation: M; analysis: M, BI; writing-original draft preparation: M; writing-review and editing: M, BI; supervision: BI; all authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTERESTS

Declared none

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