



FALSE PHARMACORESISTANCE – A TRUE PROBLEM

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SUMMARY – Pharmacoresistant epilepsy poses a great burden to patients, their families, and the whole healthcare system, with numerous social, economic, physical, and psychological consequences. Hence, it is a diagnosis that has to be made only in cases of high certainty, after all potential causes of epilepsy have been evaluated. One of the important causes of pharmacoresistant epilepsy is false pharmacoresistance, an entity that implies a condition in which poor disease control is not a consequence of the biology of the disease itself, antiepileptic drug inefficacy, and/or patient specificity. It is a consequence of human error and strongly depends on the experience of the treating physician, as well as on the attitude of the patient. Despite its 'falseness', this entity is accompanied by real consequences for the patient and his family, and at the same time, it delays appropriate treatment of the actual disease from which the patient is suffering. In order to introduce appropriate treatment and avoid unnecessary and harmful diagnostic procedures, false pharmacoresistance is a condition that has to be ruled out in any patient with difficult-to-treat seizures.

Key words: *Epilepsy; False pharmacoresistance; Antiepileptic drugs; Pharmacoresistant epilepsy*

Introduction

Despite the availability of more than twenty antiepileptic drugs (AEDs) with various mechanisms of action, in about one-third of patients (estimated to exceed 40% in some studies) epilepsy remains resistant to drug therapy¹. According to the International League against Epilepsy definition, pharmacoresistant epilepsy (PRE) is defined as a failure of adequate drug trials of two tolerated and appropriately chosen and used AED regimens to achieve seizure freedom, whether as monotherapy or in combination². The concept of pharmacoresistance implies not only intractable seizures but also structural and neurobiochemical changes with accompanying cognitive and neuropsychiatric disturbances, as well as psychosocial dysfunction³.

Patients with PRE present a heterogeneous group with a wide spectrum of clinical and neurobiological differences. Hence, the management of this specific group of patients requires commitment and a comprehensive approach to avoid all undesirable clinical scenarios, from sudden unexpected death in epilepsy (SUDEP) to misdiagnosis which can call for treatment that in some cases can be harmful.

Pharmacoresistant epilepsy poses great burden on the patients and their families but also has a huge impact on the healthcare system. Individuals who fail to respond or respond only partially to AEDs often lose their employment potential and family members are frequently forced to take on the role of a caregiver, which has an enormous impact on financial stability and social status. Moreover, frequent incapacitating seizures can lead to neuropsychological, psychiatric and social impairments, thereby reducing the quality of life and increasing morbidity and mortality⁴. Hence, it is extremely important to recognize PRE promptly. Ex-

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cept for the fact that the patient's disease fits the definition of PRE, before diagnosing PRE every physician should bear in mind the following: AED is considered effective if there is a seizure-free period of 12 months or at least three times the longest pre-treatment inter-seizure interval²; AED should be appropriately chosen for the seizure type and/or epileptic syndrome and administered for a minimum of six months⁵; and dose range and frequency of administration should be determined regarding individual response, ongoing comorbidities, AED tolerability, and possible adverse side effects⁶. After all the above facts have been taken into account, and the patient still meets the criteria, PRE can be diagnosed and the patient should be referred to one of the centers for the management of PRE.

There are numerous potential causes of PRE and when evaluating a patient with PRE, they all should be considered. Anyhow, false pharmacoresistance should be considered and excluded in any patient with difficult-to-treat seizures. The concept of false pharmacoresistance implies a condition in which poor disease control is not a consequence of the biology of the disease itself, AED inefficacy, or patient specificity. It is often a consequence of the so-called modifying causes of pharmacoresistance, which depend primarily on the physician but also on the patient. The importance of recognizing this clinically heterogeneous entity is more than apparent when considering all the potentially harmful effects of prescribed AED regimens (frequently polytherapy), all socio-economic consequences of the diagnosis of PRE, and most important, misdiagnosis and delay of appropriate treatment for the condition from which the patient is suffering. However, false pharmacoresistance may not be easily recognizable. It is estimated that up to 30% of patients referred to tertiary centers with the diagnosis of PRE may have been misdiagnosed⁷. To avoid misdiagnosis, diagnosing epilepsy (hence PRE) is a process that must include the following: differentiation of seizures from other causes of altered consciousness/awareness/behavior; distinguishing provoked from unprovoked seizures; classification of seizures; classification of epilepsy; and determination of the underlying cause⁷. Frequent diagnostic mistakes resulting in false pharmacoresistance are the consequences of failure in differentiation of seizures from seizure-like conditions and classification of seizures and epilepsy. The causes of false pharmacoresistance can be divided into three groups described below.

Diagnostic Errors

Misdiagnosis of epilepsy

Epilepsy is a diagnosis mostly based on clinical history. Incomplete history taking is one of the main obstacles in diagnosing epilepsy. Besides video electroencephalography (EEG) monitoring, the use of which is limited to specialized epilepsy centers, there is no relevant diagnostic tool that could determine whether the patient has epilepsy or not, especially in outpatient clinics. Hence, detailed and adequate history taking (which in case of the first consultation can often last for an hour or more) is a crucial step in avoiding misdiagnosis of epilepsy. In case of misdiagnosis, a trial with AED will generally fail to control the patient's condition, and he/she will continue to experience 'seizures'. Consequently, such a patient will be diagnosed with PRE. According to the literature, up to 30% of patients with PRE referred to specialized epilepsy centers, after evaluation which includes prolonged video-EEG monitoring, are diagnosed with nonepileptic seizures^{8,9}. Psychogenic nonepileptic seizures (PNES) and syncope are the most common diagnoses, however, other conditions such as atypical extrapyramidal disorders or sleep disorders are not exclusive^{10,11}.

Psychogenic nonepileptic seizures are the most important differential diagnosis of PRE, and one of the leading causes of false pharmacoresistance. PNES is a psychiatric condition, one of the presentations of a conversion disorder. It may also be present in patients with other psychiatric comorbidities such as depression, anxiety disorders, post-traumatic stress disorder (PTSD), personality disorders, as well as in cases of malingering or factitious disorder⁷. PNES is exhibited by 5%-10% of outpatients in epilepsy centers and 20%-40% of inpatients in epilepsy monitoring units^{7,12-14}. Among patients with the diagnosis of PRE, Smith *et al.* observed 13% of patients with PNES⁹. In a study of generalized convulsive status epilepticus, 10% of patients thought to have benzodiazepine-refractory generalized convulsive status epilepticus, after adjudicated review were found to have PNES¹⁵. Thus, recognizing PNES is very important to avoid unnecessary exposition to AEDs (and consequently toxicity, side effects, etc.) and the impact of the condition on the quality of life, and to initiate psychiatric treatment.

Syncope can be misdiagnosed as epilepsy, especially in cases when a brief motor phenomenon (brief

tonic phase, myoclonic jerks) is conjured with the loss of consciousness¹⁴. However, due to its characteristic temporal (often provocative) occurrence, syncope is a relatively uncommon cause of epilepsy misdiagnosis and accordingly, the misdiagnosis of false pharmacoresistance.

Seizures are a symptom of epilepsy but can also be a symptom of various other disorders. The underlying cause of the latter is not epilepsy (epileptogenic network) but the disease itself, such as celiac disease or autoimmune encephalitis. These kinds of seizures are often resistant to AEDs from the very beginning, and could easily mislead to the diagnosis of false pharmacoresistance. It is important to emphasize that in such cases, treatment of the underlying condition (or disease) may result in complete seizure cessation. Hence, in every patient with PRE, it is necessary to conduct a detailed diagnostic workup and exclude all the conditions that are not epilepsy but can result in the occurrence of seizures (Table 1).

Misdiagnosis of epilepsy type (wrong classification of seizures and syndromes)

In certain cases, it could be challenging to distinguish generalized from focal seizures. For example, so-called frontal 'pseudo-absence' seizures can resemble generalized absence seizures. Hence, it could be difficult to distinguish them from typical absence seizures of idiopathic generalized epilepsy (childhood or juvenile absence epilepsy) or atypical absences of syndromes such as Lennox-Gastaut or Dravet syndrome²⁰. Frontal 'pseudo-absence' seizures are characterized by speech and behavioral arrest, staring, reduced to complete loss of consciousness (sometimes with minor head and eye turning), and simple automatisms²⁰. They can be very short (less than 5 seconds) but may also last for 30 seconds or more, and sometimes may progress to bilateral tonic-clonic seizures. Moreover, interictal EEG with 3 Hz diffuse spike-and-slow-wave complexes could also be misleading. However, spike-and-slow-wave complexes in frontal 'pseudo-absence' are usually predominant over frontal regions, often with variable frequency (2.5 to 4 Hz). Other EEG abnormalities such as secondary bilateral synchrony (bilateral and synchronous 2 to 4 Hz discharges generated by a unilateral cortical focus), focal spikes, and paroxysms in frontotemporal regions may also be seen²⁰. Seizures that resemble absence can also be seen in

Table 1. Conditions besides epilepsy that can cause seizures¹⁵⁻¹⁹

Gastroenterology <ul style="list-style-type: none"> • Liver failure (hepatic encephalopathy) • Celiac disease • Inflammatory bowel disease • Crohn's disease
Nephrology <ul style="list-style-type: none"> • Uremic encephalopathy • Hypertensive encephalopathy • Electrolyte disturbances (hypocalcemia, hypo- or hypernatremia) • Dialysis disequilibrium syndrome • Rapid rise in hemoglobin after starting erythropoietin
Endocrinology <ul style="list-style-type: none"> • Hypoglycemia • Hyperglycemia • Electrolyte abnormalities • Inborn errors of metabolism • Pyridoxine deficiency
Neurology <ul style="list-style-type: none"> • Central nervous system infection • Autoimmune encephalitis • Paraneoplastic syndrome • Head trauma (acute seizures)
Immunology <ul style="list-style-type: none"> • Systemic lupus erythematosus • Antiphospholipid syndrome • Hashimoto thyroiditis • Sjögren's syndrome • Behçet's disease
Infections <ul style="list-style-type: none"> • Human immunodeficiency virus infection • Sepsis
Porphyria
Pharmacological agents (lithium, antidepressants, theophylline, interferons, tacrolimus, quinolones, meperidine, tramadol, etc.)
Fever (children)
Sleep deprivation
Illicit drug use (amphetamines, cocaine) and withdrawal
Alcohol use and withdrawal

temporal lobe epilepsy. However, due to their specific clinical presentation and EEG, it is much easier to distinguish them from absence seizures or *vice versa*.

Another reported cause of false pharmacoresistance due to diagnostic error is failure to recognize idiopathic generalized epilepsy, usually juvenile myoclonic epilepsy¹⁴. In this case, myoclonic jerks are misinterpreted as focal motor seizures with consequent prescription of carbamazepine (CBZ), an AED that is inefficient and can aggravate myoclonic seizures.

Anyway, it is obvious that misclassified seizures (or syndromes) direct therapy in an opposite direction, hence applied therapy does not affect disease control, which may lead to the conclusion that the patient suffers from PRE.

Therapeutic Errors

Inappropriate AED or AED combinations

The definition of pharmacoresistance requires appropriate drug trials of two tolerated and appropriately chosen and used AED regimens². After the right diagnosis, the choice of the right AED for the seizure type/syndrome is the second most important step in proper management of patients with epilepsy. During decades of pharmacological epilepsy treatment, observations have pointed to the fact that for treatment of specific seizure types and epilepsy syndromes, certain AEDs have better and others have worse or no efficacy. The more so, some AEDs can even aggravate seizures (Table 2). Consequently, the selection of inappropriate AEDs that will not be effective for certain seizure types or epilepsy syndrome can result in pharmacoresistance, which is false in such cases.

Another cause of false pharmacoresistance is an inappropriate combination of AEDs in polytherapy or a combination of AED(s) with drugs that reduce the effectiveness of AEDs due to interactions. Concomitant use of AEDs with the same mechanism of action may result in lower efficacy of both drugs. Some observations indicated lower efficacy, as well as the lack of synergistic effect of certain combinations of AEDs with the same mechanism of action²⁴⁻²⁶. Concomitant use of drugs that affect the pharmacokinetics of AEDs and thus cause their reduced efficacy, may also be the cause of false pharmacoresistance. It is well known that AEDs are a group of drugs with the potential for interactions, mostly due to predominant hepatic metabolism (CYP 450 enzymes which are prone to enzyme induction and hence more extensive metabolism of

Table 2. Examples of AEDs with the potential for aggravation of some seizure types or epilepsy syndromes²¹⁻²³

AED	Seizure aggravation
Carbamazepine	Absence, myoclonic, GTCS
Gabapentin	Absence, myoclonic, Lennox-Gastaut syndrome
Lamotrigine	Myoclonic, Lennox-Gastaut syndrome, juvenile myoclonic epilepsy, Dravet syndrome, BECTS
Levetiracetam	Absence
Vigabatrin	Absence, myoclonic, Lennox-Gastaut syndrome, Dravet syndrome
Oxcarbazepine	Myoclonic, Lennox-Gastaut syndrome, juvenile myoclonic epilepsy
Phenytoin	Absence, myoclonic, Lennox-Gastaut syndrome, juvenile myoclonic epilepsy
Valproic acid	Absence, BECTS
Tiagabine	Absence
Phenobarbital	Negative myoclonus, tonic, absence

AED = antiepileptic drug; GCTS = generalized tonic-clonic seizures; BECTS = benign epilepsy with centro-temporal spikes

specific AED). For example, in women with epilepsy taking lamotrigine (LTG), the introduction of hormonal contraceptives, known inducers of LTG metabolism, can cause a significant decrease in serum LTG levels in just a few days. This may have clinical repercussions in the form of emerging seizures, and the appearance of LTG resistance in patients with previously well-controlled epilepsy²⁷. Unfortunately, AED interactions are frequently omitted when tailoring the right therapy for the patient.

Inappropriate AED dosage

Inappropriate AED dosage is important, and not so rare, the cause of false pharmacoresistance. Irrational fear of the possible side effects could result in prescribing lower doses of AEDs, insufficient to control seizures. Adequate dose for seizure control (to control seizures) is individual, thus it is important to follow the basic principle of AED therapy, i.e. slow titrating up to the effective dose or maximal tolerable dose.

Table 3. Causes of false pharmacoresistance

Diagnostic errors	Therapeutic errors	Inadequate compliance
(a) Misdiagnosis of epilepsy <ul style="list-style-type: none"> • PNES • Syncope • Other seizure-like conditions (b) Misdiagnosis of epilepsy type (wrong classification of seizures and syndromes)	(a) Inappropriate AED or AED combinations <ul style="list-style-type: none"> • Inappropriate combinations of AEDs in polytherapy • Combining AED(s) with other drugs that affect the pharmacokinetics of AEDs and reduce their efficacy (b) Inappropriate AED dosage	Non-adherence to treatment <ul style="list-style-type: none"> • Skipping doses or not taking medication • Self-initiated changes in the regimen of taking or changing dose

AED = antiepileptic drug; PNES = psychogenic nonepileptic seizures

Due to the potential drug interactions and fear of side effects, therapeutic regimens involving two, three and even more AEDs could represent an additional cause of inadequate AED dosing in some patients. In such cases, one or more often all AEDs are prescribed at the doses lower than the recommended maintenance doses. Consequently, there is an increased risk of continuous seizures and hence the diagnosis of PRE, as well as the risk of adverse events or side effects due to AED interactions or idiosyncratic reactions. In their study, Smith *et al.* observed patients who had never, during their history of epilepsy, received adequate doses of AED⁹.

Another potential cause of false pharmacoresistance is injudicious reliance exclusively on therapeutic serum range during AED dose adjustment. Adequate dose for achieving seizure freedom is individual and varies from patient to patient. Some patients do well below the lower limit of 'therapeutic range', whereas others may require and tolerate higher levels without toxicity²⁸. Therapeutic range represents the dosage range expected to achieve a desired therapeutic effect in most but not all patients. Thus, AED dose adjustment should be based mostly on clinical parameters.

However, serum AED concentrations may be helpful in certain conditions, primarily in case of suspected AED toxicity, during pregnancy due to physiologically altered metabolism of certain AEDs (especially lamotrigine), and also in case of suspected non-compliance.

Inadequate Compliance

Patient decisions and behaviors are very important factors in successful epilepsy treatment. Non-adherence to the treatment regimen is the fact of which every

physician should be aware, especially when evaluating PRE. In a study that included 661 patients with epilepsy, 71% of patients skipped a dose of AED at least once during therapy²⁹. It is important to emphasize that non-adherence to the therapeutic regimen does not only mean skipping or not taking medication but also self-initiated changes in the regimen of taking or changing the dose of medication. Factors that affect adherence to the treatment regimen comprise the relationship between the patient and his physician, the level of social support, age, belief in therapy, level of knowledge about their disease, frequency of seizures, and frequency of daily AED doses³⁰⁻³³. There are many methods for monitoring compliance, and they include measuring serum AED concentrations, counting remaining tablets/capsules, digital records in pharmacy databases, and self-reporting (therapy diaries, digital drug monitoring platforms, etc.). It is important to emphasize that all these methods have limitations, hence the most reliable way to monitor compliance is the patient word. The consequences of non-compliance in patients with epilepsy can be quite dangerous, in some cases fatal, and it is indisputable that they significantly affect the quality of life. Forgetfulness, negligence, or intentional concealment of non-compliance with the treatment regimen can mislead the clinician to the conclusion on inadequate disease control and consequently result in modification of therapy, and in some cases diagnosis of PRE. This is quite worrying and imposes the importance of clear communication and building trust between the patient and his physician.

Conclusion

Physicians managing patients with epilepsy must be aware of false pharmacoresistance since misdiagno-

sis of PRE has numerous consequences, including physical, psychological, social, as well as economic implications for health services. In the study by Smith *et al.*, the most commonly observed causes of false pharmacoresistance were suboptimal use of AEDs, poor compliance, and failure to appropriately classify epilepsy⁹. Unnecessary exposure to AEDs (in case of suspected PRE, often used as polytherapy) poses a risk of toxic adverse effects, idiosyncratic or hypersensitivity reactions, and also of drug-induced congenital malformations in women of childbearing age, while suboptimal use of AEDs resulting in frequent seizures poses a risk of seizure-related injuries, as well as SUDEP. The lack of awareness of epilepsy classification is the main reason for the suboptimal management of patients with epilepsy⁹. Hence, thorough education of medical staff dedicated to epilepsy treatment could reduce the impact of wrong seizure or epilepsy classification on patient management. Poor compliance as the cause of false pharmacoresistance is the issue that is most difficult to resolve. However, with a dedicated physician ready to build a trustful relationship with his patient, non-compliance should not be an issue. Since false pharmacoresistance is strictly dependent on the human factor, continuous education of medical staff, with the ultimate goal of removing this entity from the list of potential causes of PRE, is mandatory.

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Sažetak

LAŽNA FARMAKOREZISTENCIJA – STVARNI PROBLEM

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Farmakorezistentna epilepsija, dijagnoza koju prate brojne društvene, ekonomske, fizičke i psihičke posljedice, predstavlja veliko opterećenje za bolesnike, njihove obitelji, ali i cjelokupni zdravstveni sustav. Stoga je farmakorezistentnu epilepsiju opravdano dijagnosticirati samo u slučajevima u kojima je liječnik siguran u dijagnozu nakon što su procijenjeni svi mogući uzroci. Jedan od uzroka farmakorezistentne epilepsije je takozvana lažna farmakorezistencija, entitet koji podrazumijeva stanje u kojem loša kontrola bolesti nije posljedica biologije same bolesti, antiepileptičkih lijekova i karakteristika bolesnika. Ona je posljedica ljudske pogreške i izravno ovisi o iskustvu liječnika koji liječi, ali i o stavu bolesnika prema liječenju. Unatoč „lažnosti“ ovaj entitet prate stvarne posljedice za bolesnika i njegovu obitelj, a istodobno odgađa odgovarajuće liječenje stvarne bolesti od koje bolesnik boluje. Kako bi se osiguralo uspješno liječenje te izbjegli nepotrebni i štetni dijagnostički postupci, lažna farmakorezistencija je stanje koje se mora isključiti kod svakog bolesnika s epileptičkim napadajima koji se teško kontroliraju.

Ključne riječi: *Epilepsija; Lažna farmakorezistencija; Antiepileptički lijekovi; Epilepsija otporna na lijekove*