

## **Which terms should be used to describe medications used in the treatment of epilepsy? An ILAE position paper**

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## **Abstract**

Historically, medications used in the treatment of epilepsy have been referred to by a variety of terms, such as ‘antiepileptic’, ‘anticonvulsant’, or ‘antiseizure’. Terminology is important, because using terms which do not reflect accurately the action of specific treatments may result in misunderstanding of their effects and inappropriate use. The present ILAE position paper used a Delphi approach to develop recommendations on the terminology applicable to pharmacological agents currently approved for the treatment of seizure disorders. There was consensus that these medications should be collectively named as ‘antiseizure medications’ (ASMs). This term reflects accurately their primarily symptomatic effect against seizures, and reduces the possibility of healthcare practitioners, patients or caregivers having undue expectations, or an incorrect understanding of the real action of these medications. The term ‘antiseizure’ to describe these agents does not exclude the possibility of beneficial effects on the course of the disease and comorbidities that result from downstream effects of seizures, whenever these effects can be explained solely by suppression of seizure activity. It is acknowledged that other treatments, mostly under development, can exert *direct* favorable actions on the underlying disease or its progression, by having ‘antiepileptogenic’, ‘antiepileptic’ or ‘disease modifying effects’. A more refined terminology to describe precisely these actions needs to be developed.

**Key words:** Antiseizure medications, Antiepileptic drugs, Terminology, Recommendations

**Key points:**

- The terminology used to describe treatments should reflect accurately the nature of their primary action
- Because medications currently used in the treatment of epilepsy exert a symptomatic effect against seizures, they should be referred to as 'antiseizure medications' (ASMs)
- The term 'antiseizure' does not exclude the possibility of suppression of seizure activity having a favorable influence on the course of the disease and on comorbidities that result from downstream effects of seizures
- A more refined terminology needs to be developed to describe treatments, mostly under investigation, that have direct (seizure-unrelated) actions on the underlying disease process leading to seizures or its progression

## 1 INTRODUCTION

Since the original description by Sir Charles Lockock in 1857 of the clinical effectiveness of potassium bromide in controlling seizures in women with epilepsy, over 40 medications have been introduced for the treatment of epilepsy.<sup>1,2</sup> Historically, these medications have been referred to in the medical literature by a variety of terms, such as ‘antiepileptic’, ‘anticonvulsant’, or ‘antiseizure’. Names matter, and some of those terms have increasingly come under criticism. For example, the use of the name ‘anticonvulsant’ to collectively denote these medications is less than appropriate, because not all seizure types are convulsive.<sup>3</sup> Likewise, the term ‘antiepileptic drug’ (AED), while still widely used, has been considered inaccurate<sup>3,4,5</sup> because currently used medications are purely symptomatic therapies, i.e. they suppress the symptoms (seizures) but have no demonstrated direct activity on the underlying disease (epilepsy).<sup>6,7</sup> It has also been argued that in some settings the term ‘anti-epileptic’ has stigmatizing undertones, as it could be perceived as hostile to an ‘epileptic’, i.e. a person with epilepsy.<sup>4</sup> Other arguments have been raised against use of the term ‘drugs’, which in the English medical literature can be used interchangeably with ‘medicines’ or ‘medications’ but in community settings (and in its literal translation into other languages) can be extended to denote compounds associated with non-therapeutic, illegal recreational abuse and dependence.<sup>4</sup> In view of these considerations, the terms ‘antiseizure medicines’ or ‘antiseizure medications’ have been regarded as being more appropriate, and indeed these terms have been increasingly used in recent medical literature.<sup>3,5</sup> Use of etymologically correct terminology becomes particularly important in the current era, when efforts are ongoing to identify and develop novel treatments that do not have a purely symptomatic effect against seizures, but may actually treat underlying pathophysiology leading to epilepsy, prevent the occurrence of epilepsy or modify its course.<sup>8-10</sup>

Based on the above background, the International League Against Epilepsy (ILAE) considered it necessary to provide guidance on appropriate terminology to describe treatments that are currently available or may become available in the future. The present position paper from the ILAE Nomenclature Task Force provides recommendations on the terminology to be applied to pharmacological treatments that exert a symptomatic effect against seizures.

## 2 METHODS

Consensus on the recommended terminology was achieved using a modified Delphi process.<sup>11</sup> The Delphi panel, that included all 16 members of the Nomenclature Task Force, was appointed by the ILAE Executive Committee in consultation with the Task Force co-chairs (EP and JF). Membership included representation from every ILAE region, from the International Bureau for Epilepsy (IBE), and from clinical as well as basic science expertise.

To finalize the key statements of the consensus paper, an iterative approach was used. First, a set of 16 statements drafted by the Nomenclature Task Force co-chairs and worded to ensure relevance to the goal were submitted via electronic survey to the panel members, who were given the opportunity to propose additional statements. Two additional statements were proposed at this stage, bringing the total to 18. A link to each statement was then sent electronically to each panelist, whose responses were anonymous. Panelists rated each statement on a 9-point Likert scale from 1 (“strongly disagree”) to 9 (“strongly agree”) with a no judgement option to reflect “no opinion”. Panelists were given the opportunity for comments, particularly if they did not agree with the concept expressed by the statements or their wording. According to a predefined

procedure, statements that received median ratings of 3 or less without discordance (defined as >25% of panelists rating the statement 7 or higher) were to be discarded. Statements with median ratings of 7 or higher without discordance (defined as >25% of panelists rating the item as 3 or lower) were accepted. Statements with median ratings of 4-7, or those showing discordance, were reviewed by the co-chairs, reworded based on the feedback received by panelists and resubmitted for a second round of ratings. Items that did not achieve consensus following the second round could be adjudicated by the co-chairs following consideration of any further comments received, but no adjudication was needed because consensus on each of the 18 items was achieved at the end of the second round.

The finalized statements, and associated ratings for level of agreement (Table 1), provided the basis for the compilation of the consensus document, which was approved by all co-authors.

### **3 RECOMMENDATIONS**

#### **3.1 ‘Antiseizure’ as preferred term for medications having a symptomatic effect**

There was consensus within the Task Force that most medications currently used to treat epilepsy exert their effects by suppressing the symptoms (seizures). In fact, these medications have been approved by regulatory authorities based solely on the evidence of a symptomatic effect on seizure activity. Therefore, the term ‘antiseizure’ is the most appropriate term to describe these medications. The Task Force considered that the term "antiseizure" is sufficiently explanatory in the English language, and that including the term ‘epileptic’ when describing the effect of these medications is redundant.

#### **3.2 ‘Seizure’ versus ‘epileptic seizure’**

The Task Force also determined that in the English language the term ‘seizure’ should preferably be reserved to indicate ‘epileptic seizures’, and preferably avoided when describing non-epileptic events. On the other hand, it was acknowledged that in other languages, the term ‘epileptic’ may need to be retained when referring to epileptic seizures, in order to avoid misinterpretation.

#### **3.3 ‘Medication’ versus ‘medicine’ or ‘drug’**

The Task Force also discussed alternatives to the term ‘medication’. ‘Medication’ in the English language refers only to therapeutic products, whereas "medicine" is used to indicate both the science of treating symptoms/diseases as well as the products used to treat these conditions. This may justify a preference for the term ‘antiseizure medication’ (ASM), although both ‘medication’ and ‘medicine’ can be used interchangeably in this context. On the other hand, the term ‘antiseizure drug (ASD)’ is not recommended because the acronym ‘ASD’ is a widely established to indicate autism spectrum disorder, and is also used in cardiology as shorthand for an atrial septal defect.

#### **3.4 When should the term ‘antiepileptic’ be used?**

Use of the term ‘antiepileptic’ is not recommended when describing medications which have a purely symptomatic effect. The Task Force acknowledged that a medication that alters the symptom of seizure, by providing seizure control (including suppression of epileptic EEG discharges), can have an *indirect* favorable impact on other outcomes such as cognitive development and, possibly, susceptibility to further seizures. Any such favorable effect on the underlying disease, however, could be solely a consequence of symptom suppression. In fact, using the term ‘antiepileptic’ in this setting may mislead people with epilepsy, their caregivers, the lay public and health professionals into believing that these medications treat more than just the symptoms of the disease, and that disappearance of the symptoms could necessarily signal disappearance of the underlying disease.

The Task Force considered that the term "antiepileptic" should be reserved for medications that have been demonstrated to have a *direct* effect on the course of epilepsy, the likelihood of developing epilepsy, or the likelihood of developing more severe epilepsy. Applying the term "antiseizure" to treatments which have symptomatic effects does not exclude that the same treatments may have, in addition, *direct* actions on the underlying epilepsy, epileptogenic processes or co-morbidities. For example, a medication could have antiseizure effects, and have an independent effect on epileptogenesis. Therefore, the term ‘antiseizure’ and ‘antiepileptic’ should not be regarded as being mutually exclusive.

### **3.5 Application to non-pharmacological treatments**

Appropriate terminology (antiseizure, antiepileptic or appropriate alternatives) also should be used to describe not only pharmacological treatments (medications), but also the actions of other therapeutic modalities such as surgery, neurostimulation and dietary treatments.

### **3.6 Language-specific issues**

Although the remit of our Task Force was to develop recommendations for English-language terminology, we acknowledge that there is a need for a similar effort to be applied to development of correct terminology in all other languages. Accordingly, the ILAE encourages the development at the regional and national level of corresponding terminology in languages other than English, taking into consideration the specific social and cultural context and the need for broad stakeholders’ involvement.

## **4 DISCUSSION AND CONCLUSIONS**

The terms used to describe diseases and their treatment carry important medical and social implications. This is particularly true when dealing with diseases such as epilepsy that are commonly associated with misperception, prejudice and stigma, all of which could be affected by how specific terms are interpreted by health professionals, patients and the public at large.<sup>12</sup> Accordingly, recommendations concerning specific terminology should be undertaken in consultation with all stakeholders involved. The present position paper was developed through involvement of healthcare professionals with disparate expertise and geographical location, as well as representation from the IBE, the leading lay organization representing people with

epilepsy. The paper also incorporates feedback obtained by public consultation with members of the ILAE and IBE communities.

Ideally, the terminology used to describe therapeutic agents should reflect accurately the nature of their primary action. Based on this principle, the medicines currently used in the treatment of epilepsy should be collectively described by the term ‘antiseizure medications’ or ‘anti-seizure medications’ (ASMs), which may be used interchangeably though the term without hyphen may be preferred for simplicity. This term, which has been increasingly used in recent years<sup>5</sup>, reflects accurately their primarily symptomatic effect against seizures, and reduces the possibility of healthcare practitioners, patients or caregivers having undue expectations, or an incorrect understanding of the real action of these medications. These medications may be further categorized by classifying them according to their molecular mechanism(s) of action, which could be relevant for their rational clinical use.<sup>13,14</sup> Of note, the term ‘antiseizure’ to describe these agents does not exclude the possibility of a favorable influence on the course of the disease and associated comorbidities, as long as these beneficial effects can be explained solely by suppression of seizure activity. For example, rapid achievement of seizure control in children with epileptic encephalopathies often impacts favorably on cognitive outcome, an effect that can be simply ascribed to cessation of epileptic discharges and their consequent damaging effect on the developing brain.<sup>15</sup> The possibility that some treatments do or will exert direct favorable effects on the underlying disease or its progression is acknowledged. One example of treatments that target the underlying pathophysiology are the immune therapies used to treat autoimmune epilepsies, which often respond poorly to conventional antiseizure medications.<sup>16</sup> Extensive preclinical and clinical research aimed at developing innovative treatments with disease-modifying, antiepileptic or antiepileptogenic activity is ongoing. A more refined terminology will be needed to precisely describe the actions of these innovative interventions.

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## **CONFLICT OF INTEREST**

S. Balestrini received consulting fees from Biocodex, Eisai and UCB Pharma.

P. Braga reports that her Institution received research support from Roemmers and support for educational material from GlaxoSmithKline.

J. A. French receives salary support from the Epilepsy Foundation and for consulting work and/or attending Scientific Advisory Boards on behalf of the Epilepsy Study Consortium for Adamas,



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A. S. Galanopoulou is the Editor-in-Chief of *Epilepsia Open* and associate editor of *Neurobiology of Disease* and receives royalties from Elsevier, and Medlink for publications.

S. H. Lim received speaker fees from Eisai.

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R. Nabbout has served as principal investigators in clinical trials for Novartis, Nutricia, Eisai, UCB, GW Pharma, Livanova. She received consulting fees from Biogene, BioMarin, GW Pharma, Zogenix, Novartis, Nutricia, Stoke, Ionis, Targeon, Takeda and honoraria from Nutricia, Biocodex, Zogenix, GW Pharma, Supernus, Neuraxpharm, Advicenne and Eisai. She received unrestricted research grants from Eisai, UCB, Livanova, Zogenix and GW Pharma and academic research grants from EJP-RD, European reference network for rare diseases. She is holder of Geen-DS Chair supported by the « FAMA Fund hosted by Swiss Philanthropy Foundation » institute Imagine supported by the « FAMA Fund hosted by Swiss Philanthropy Foundation ».

E. Perucca received speaker and/or consultancy fees from Angelini, Arvelle, Biogen, Eisai, GW Pharma, PMI Life Science, Sanofi group of companies, SK Life Science, Sun Pharma, Takeda, UCB Pharma, Xenon Pharma and Zogenix and royalties from Wiley, Elsevier and Wolters Kluwers.

F. Sofia reports that she directed a project for the Italian Epilepsy Federation (FIE), for which FIE received support from UCB that included her compensation.

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S. Wiebe has received research support- from the Canadian Institutes of Health Research and Alberta Innovates Health Solutions. He chairs the Clinical Research Unit at the University of Calgary, which receives support from Cumming School of Medicine. His institution has received unrestricted educational grants from UCB Pharma, Eisai, and Sunovion.

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E. Wirrell has served as a paid consultant for Encoded Therapeutics and Biomarin. She is the Editor-in-Chief of Epilepsy.com.

S. Jain and Ch. Triki report no conflicts of interest.

## **GUIDELINE AFFIRMATION**

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Table 1. List of statements in their final (approved) wording. Percentage agreement (percentage of ratings in the 7-10 range) achieved during the Delphi process for each statement is shown in parentheses.

Statement #	Statement (percent of agreement)
1	Terms used to describe classes of therapeutic agents should convey at best the nature of their primary therapeutic action (100%)
2	Terms used to describe classes of therapeutic agents have implications, including potential association with stigma on how their use is perceived by health professionals, patients and the lay public at large. Therefore, the views of different stakeholders should be considered when making recommendations about applicable terminology (100%)
3	Most of the medications currently used to treat epilepsy exert their effect by suppressing the symptoms of epilepsy (seizures) and are approved based on evidence of a symptomatic effect on seizure activity and therefore the term 'antiseizure' is the most appropriate term to describe medications that alters or suppress the symptom of seizure, either in persons with epilepsy, or in persons with symptomatic seizures (87%)
4	In the same way as it is correct to use the term 'antiseizure medications' to describe drugs which act primarily by suppressing seizures, it is appropriate to say that such medications have antiseizure actions, or antiseizure effects (87%)
5	The term "anti-epileptic medication" is not recommended for a medication that suppresses the symptom of seizure and only indirectly (through seizure suppression) may affect the underlying disease (epilepsy) or comorbidities (94%)
6	The term "anti-epileptic medication" should be reserved for drugs that have been demonstrated to have a direct effect on the course of epilepsy, the likelihood of developing epilepsy, or the likelihood of developing more severe epilepsy (94%)
7	The terms "antiseizure medication" and "antiepileptic medication" are not mutually exclusive (80%)
8	It is understood that a medication that alters the symptom of seizure, by providing seizure control (including suppression of epileptic EEG discharges) can impact positively on other measures such as cognitive development and, possibly, susceptibility to further seizures (93%)
9	Use of the term "antiepileptic" when referring to these drugs may mislead people with epilepsy, their caregivers, the lay public, and some health professionals into believing that these drugs treat the disease, and that disappearance of the symptoms could necessarily signal disappearance of the underlying disease (88%)
10	Applying the term "antiseizure" to treatments which have symptomatic effects does not exclude that the same treatments may have additional actions on the underlying epilepsy, epileptogenic processes or co-morbidities. For example, a medication could have antiseizure effects, and have an independent effect on epileptogenesis (80%)
11	When referring to treatments used in the management of epileptic seizures, the term "antiseizure" may be sufficiently explanatory in the English language, and including the term 'epileptic' when describing the effect of medications adds unnecessary redundancy. In other languages, the term 'epileptic' may need to be retained, which may justify recommending the wording 'anti-(epileptic, optional) seizure (94%)
12	To minimize potential misunderstanding in English language, the term "seizure" should preferably be reserved to indicate "epileptic seizures." In other languages, the term "epileptic seizures" can be used as necessary (94%)
13	The acronym for "antiseizure drugs" is ASDs, which is a widely used acronym to indicate autism spectrum disorder. Therefore, "antiseizure medicines (ASMs)" or "antiseizure medications (ASMs)" is the preferred choice (93%)

14	"Medication" refers more specifically to therapeutic products, whereas "medicine" is used to indicate both the science of treating diseases as well as the products used to treat disease (93%)
15	Although the remit of the Task Force is to make recommendations about English-language terms, the Task Force realizes that the issue has high relevance in all languages (100%)
16	Regional and national stakeholders within the ILAE organization should be encouraged to take appropriate action to address the issue and make recommendations about adequate terminology to be applied in their local language(s), taking into consideration the specific social and cultural context and the need for broad stakeholders' involvement (93%)
17	Among drugs with antiseizure effect, grouping and naming according to their major mechanism of action would be a further step of potential clinical benefit (e.g. helping the clinician to design a rational polytherapy), while taking into account their frequent clinical use in other, unrelated conditions (80%)
18	Although exceeding the scope of this Task Force, and in order to help lay people understand treatment algorithms in epilepsy, similar considerations may apply to treatment modalities other than drugs (e.g. surgery, stimulation, diet); once defined their mechanism of action and/or impact, they should be included in the corresponding "antiseizure", "anti-epileptic" or other category of treatment (93%)