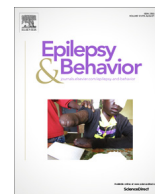




Contents lists available at ScienceDirect

## Epilepsy &amp; Behavior

journal homepage: [www.elsevier.com/locate/yebeh](http://www.elsevier.com/locate/yebeh)

## Selection of antiseizure medications for first add-on use: A consensus paper



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### ARTICLE INFO

#### Article history:

Received 20 March 2021

Revised 21 May 2021

Accepted 22 May 2021

#### Keywords:

Antiepileptic drugs

Epilepsy

Treatment

Adjunctive therapy

Drug selection

### ABSTRACT

**Introduction:** When monotherapy used alone or sequentially fails to achieve seizure control, a trial of combination therapy may be considered.

**Objective:** To define optimal criteria to guide choice of an antiseizure medication (ASM) for use as first add-on.

**Methods:** A standardized Delphi procedure was applied to produce a list of consensus statements. First, an Expert Board consisting of 5 epileptologists agreed on a set of 46 statements relevant to the objective. The statements were then finalized through an iterative process by a Delphi Panel of 84 Italian pediatric and adult neurologists with expertise in the management of epilepsy. Panel members provided anonymous ratings of their level of agreement with each statement on a 9-point Likert scale.

**Results:** Consensus, defined as agreement by at least 80% of Panel members, was reached for 36 statements. Medication-related factors considered to be important for drug selection included efficacy, tolerability and safety, interaction potential, mechanism of action, and ease of use. The need to optimize adherence and to tailor drug selection to individual characteristics was emphasized.

**Conclusions:** Choice of an ASM for first add-on requires consideration of many factors, many of which also apply to choose initial treatment. Factors more specifically relevant to add-on use include drug interaction potential and the preference for an ASM with a different mechanism of action.

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## 1. Introduction

Seizures in approximately 50% of patients with epilepsy are not completely controlled with initially prescribed antiseizure medication (ASM) [1]. Subsequent treatment options for these patients include switching to monotherapy with an alternative ASM, or adding another medication. Small randomized controlled trials that evaluated the relative merits of alternative monotherapy and combination therapy in patients unresponsive to a single ASM did not identify a clear superiority of one option over the other [2,3], and it has been suggested that optimal management

strategy may vary in relation to the characteristics of the patient and the properties of the medications being assessed [3–5]. When sequential monotherapies failed, however, most physicians are likely to resort to a trial of combination therapy [4,6]. In fact, combinations of ASMs are widely used in patients with uncontrolled seizures [4]. The potential value of this approach is justified by evidence that polytherapy is not necessarily associated with a higher burden of adverse effects compared with single drug therapy [5].

Selection of ASMs in patients with uncontrolled seizures is generally based on consideration of individual characteristics such as seizure type, epilepsy syndrome, age, gender, lifestyle, expected compliance, and patient's expectations [4,5]. Other relevant variables include concomitant medications, with the attendant risk of adverse drug interactions, and comorbidities, which could be influenced adversely or beneficially depending on the ASM that is chosen [6].

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The same factors need to be considered when selecting an ASM as first add-on therapy for individuals who did not respond optimally to a single or a sequential monotherapy. In this situation, however, additional variables need to be taken into account, including response to previously administered ASMs, and the possibility of pharmacodynamic and/or pharmacokinetic interactions between the ASMs to be combined [7–9]. The application of these considerations in drug selection has been proposed to provide the basis for so-called “rational polytherapy” [9,10].

In the last 30 years, 18 second-generation ASMs have been added to the therapeutic armamentarium against epilepsy [11]. The availability of a large number of medications, many of which are only approved for adjunctive therapy, offers unprecedented opportunities to tailor treatment choice to individual characteristics. However, it also complicates drug selection, especially for add-on therapy, due to the many possible two-drug combinations and the lack of evidence from well-designed comparative trials on how ASMs should be optimally combined. Based on this background, we considered useful to produce a consensus document on the criteria to be applied in selecting an ASM for initial (first) add-on use in patients inadequately controlled by a monotherapy regimen, and to identify medication characteristics that are optimal for such use. To achieve this objective, we applied a Delphi technique, which is a widely accepted methodology to integrate expert opinions where direct evidence from well-designed studies is lacking or controversial [12].

## 2. Materials and methods

### 2.1. General overview and structure of the Delphi process

The Delphi process adopted to produce the consensus document utilized a stepwise approach [13–15]. First, an Expert Board of five neurologists with complementary expertise and experience in the management of patients with epilepsy (a clinical pharmacologist, two adult and two pediatric epileptologists) generated a list of statements relevant to objective. The statements were then submitted to a Delphi Panel of 84 neurologists, who provided feedback on each of the statements through an iterative process that contributed to the fine tuning of the statements. In this process, Panel members rated their level of agreement with each of statements as well as their clinical relevance. The finalized statements, and associated ratings for level of agreement and relevance, provided the basis for the compilation of the consensus document.

All participants freely accepted to contribute to the project and to permit public dissemination of the results, while preserving the anonymity of individual ratings. Ethics Committee approval was not required because the project was limited to a survey and discussion of factors affecting therapeutic practice.

### 2.2. Preparation of the questionnaire

An initial set of statements was assembled by Expert Board members through a series of on-line and email interactions. Each statement was debated and modified to reflect accurately the members' knowledge and experience. Although it was acknowledged that cost of medications and reimbursement considerations may need to be taken into account in treatment selection, there was agreement to limit statements to health-related issues without inclusion of pharmacoeconomic considerations. A total of 46 statements grouped into different sections/domains were formulated and worded to ensure that they were all relevant to the goal, and that all appropriate domains were covered adequately. The statements were submitted to the Delphi Panel, finalized, and rated according to the procedure summarized below.

### 2.3. Survey procedures

A total of 125 neurologists experienced in epilepsy management were invited to participate and, of those, 84 agreed to be included in the Delphi Panel (Appendix 1). Of the 84 Panel members, 82 (96%) had been involved in the care of patients with epilepsy for >5 years, 61 were adult neurologists and 24 were pediatric neurologists. Their geographical distribution covered all regions of Italy. Prior to their participation, each Panel member was provided with standardized information about the goal of the project and details about the process, together with a list of 57 articles related to the topic. The articles were selected by the Expert Board among those considered of particular relevance, following a Pubmed search using as keywords ‘epilepsy treatment’ or ‘antiepileptic drugs’ and ‘add-on’ and/or ‘combination therapy’ and/or ‘drug selection’.

All the statements prepared by the Expert Board were submitted to the Delphi Panel members via a web-based platform. Panel members were requested to provide their ratings independently and anonymously through three consecutive rounds of consultation [16]. The statements were displayed to participants in random order to avoid sequence bias. In the first round, Panel members indicated their level of agreement with each statement using a 9-point Likert scale ranging from 1 (‘totally disagree’) to 9 (‘totally agree’). Consensus on each statement was considered to exist when as at least 80% of ratings were within the 7–9 bracket [13]. Whenever consensus was not reached for a given statement in the first round, that statement (with any associated comments) was reassessed by the Expert Board, reformulated to improve clarity, and resubmitted to Delphi Panel members in a second round. The 11 resubmitted statements underwent the same assessments and ratings to determine the final level of agreement.

After completion of the second round, Delphi Panel members were approached again and asked to rate the clinical relevance of each statement for the purpose of selecting the first add-on medication in everyday clinical practice. Ratings of relevance were made on a three-point Likert scale (1 = low, 2 = intermediate and 3 = high relevance).

The overall results of the process were discussed by the Expert Board and provided the consensus opinions used to finalize the present article.

### 2.4. Statistical analysis

The online survey platform used for the different rounds of the process was managed by an independent non-clinical administrator (BA) with expertise in Delphi techniques. A database containing all ratings provided by participants was created using a Microsoft Excel sheet. Distribution of ratings and their positioning within each pre-determined bracket were calculated to determine level of consensus. Means of ratings for each statement were also calculated. Calculations were performed using the Microsoft Office software (Microsoft Corporation, Redmond, WA, USA).

## 3. Results

### 3.1. General considerations

Of the 84 Panel members who took part in the project, 74 (87%) completed all rounds of the process. The appropriateness of the initial 46 statements was first discussed, and no additional issues/statements were proposed by the Panel. Eleven statements did not reach consensus in the first round and were reformulated and resubmitted for re-assessment. Of the reformulated statements, one reached consensus in the second round, whereas for

the remaining 10 statements the threshold required to define consensus (agreement by  $\geq 80\%$  of Panel members) was not reached (supplementary Tables 1–3). Therefore, at the completion of the process, consensus was achieved for 36 (78.3%) of the 46 statements. All statements received a rating for relevance above 2 (on 3-point scale), with 41 statements (89.1%) receiving a rating of 2.5 or greater (supplementary Tables 1–3).

There was consensus among Panel members that the primary objective of treatment should be achievement of a good quality of life. There was also consensus that efficacy and safety are primary considerations in selecting an ASM for first add-on use, and that whenever feasible a simple treatment regimen should be used (supplementary Table 1). Statements applicable to specific areas which were considered particularly relevant for treatment decision are discussed below.

### 3.2. Key factors to be considered in selecting an ASM as first add-on treatment

#### 3.2.1. Efficacy considerations

There was broad consensus among Panel members that in some patients combination therapy may be necessary to achieve a satisfactory response, and that choice of medication(s) should aim at ensuring protection against the patient's seizure type, keeping in mind the possibility that certain ASMs may have a precipitating effect on other seizure types (supplementary Table 1). There was also consensus that when seizure freedom cannot be achieved, prevention of those seizures that are more hazardous or disabling should be prioritized. The Panel agreed that a broad-spectrum ASM is more likely to be efficacious when there is uncertainty about the classification of the epileptic event, e.g., uncertainty on whether seizures are focal or generalized. It was acknowledged that certain ASMs may have beneficial effects on some comorbidities, and that this information should be taken into consideration when selecting a medication.

#### 3.2.2. Tolerability and safety

Together with efficacy, tolerability and safety were recognized as major considerations when selecting an ASM for add-on use (supplementary Table 1). Although it was broadly agreed that the side effects of medications influence quality of life in people with epilepsy, the statement that in patients with uncontrolled epilepsy the adverse drug effects are more important than seizures in reducing quality of life failed to reach consensus. The need to inform individuals with epilepsy and/or their caregivers about potential adverse effects was widely acknowledged.

There was consensus that physicians need to consider the risk of adverse effects in relation to the clinical history and other characteristics of the individual. In particular, avoidance of medications often associated with allergic reactions was considered desirable for patients with a history of immune-mediated adverse drug reactions. The need to evaluate patients carefully with respect to potential adverse effects affecting cognition, mood, behavior, cardiac function, and body weight was widely acknowledged. For females of childbearing potential, the availability of information about maternal and fetal risks associated with drug exposure during pregnancy was rated as highly relevant when selecting a medication for first add-on use. The fact that available ASMs differ in their adverse effect profile was widely acknowledged, as also indicated by the fact that there was no consensus on the proposition that the drug treatment of epilepsy is associated with common class-related adverse effects. The statement that the tolerability profile of ASMs is also influenced by the patient's characteristics and earlier life experiences was supported by over 75% of Panel members but failed to achieve the threshold majority that defines consensus.

#### 3.2.3. Drug interactions

There was broad consensus that a drug's interaction potential is a relevant factor for consideration when selecting a medication for first add-on use (supplementary Table 2). The fact that drug interactions in epilepsy can be bi-directional and that they can involve both ASMs and drugs used for other indications was broadly acknowledged. There was consensus among Panel members that physicians should be especially aware of potentially adverse drug interactions, that using ASMs in combination requires careful evaluation of the dosage of each drug in the treatment regimen, and that some ASM combinations can be advantageous because of potentially synergistic therapeutic effects.

Overall, there was consensus that, when selecting ASMs for first add-on use, preference should be generally given to drugs which have a lower potential for adverse drug interactions. However, the suggestion that ASMs devoid of enzyme inducing properties should be preferred when fully appropriate alternative treatments exist was supported by a large majority of Panel members but failed to achieve consensus by a narrow margin (supplementary Table 2).

#### 3.2.4. Mechanisms of drug action

There was consensus that when satisfactory efficacy cannot be achieved with an appropriate dosing schedule of a single ASM, an alternative medication with a different mechanism of action, used sequentially or in combination, represents a rational treatment strategy (supplementary Table 2). Panel members also agreed that co-administration of ASMs with the same mechanism of action entails a greater risk of inducing adverse effects associated with that mechanism. Both these statements were considered to have high relevance.

One of the statements questioned whether in specific settings use of an ASM possessing multiple modes of action offers any real advantage over ASMs acting selectively by a single mechanism. Panel members had divided positions on this issue, which was not rated as having high relevance (Table 3).

#### 3.2.5. Adherence issues

There was consensus that, prior to prescribing a first add-on ASM (or making a diagnosis of pharmacoresistance), the possibility of non-adherence needs to be excluded (supplementary Table 3). An effective communication between physician and patient and use of a simple dosing regimen were acknowledged to be among the factors facilitating a good adherence. The Panel agreed that adherence is influenced by a patient's concerns and expectations about adverse drug effects, and by their frequency and severity. On the other hand, there was no consensus that adherence is influenced by the extent to which a patient and/or caregiver is disturbed by continuing seizures, or by a patient's reluctance to take ASMs in a public setting.

Easy access to an assay to measure plasma drug levels was considered an important tool for the assessment of adherence. Most Panel members agreed that use of ASMs with a long plasma half-life protects against the risk of therapeutic response should a single dose be missed, but the level of support to that statement was insufficient to achieve consensus.

#### 3.2.6. Ease of use of the medication and monitoring procedures

The Panel agreed that the feasibility of a simple titration scheme that permits to achieve the target dose relatively rapidly is a desirable feature for an ASM being considered for first add-on use (supplementary Table 3). Additional medication features that were considered advantageous were feasibility of once daily dosing, feasibility of administration by different routes, and availability of both liquid and solid dosage forms. Finally, there was agreement that there are advantages in using ASMs which do not

require repeated blood chemistry, hematology, or other safety monitoring tests, even though there was no consensus that such tests can be a cause of disturbance or discomfort for the patient.

Despite the fact that the measurement of plasma drug levels was considered a useful tool for the assessment of adherence, the proposition that therapeutic drug monitoring can improve clinical management was supported by over 70% of Panel members but did not reach the threshold that defines consensus.

#### 4. Discussion

We applied a Delphi procedure to finalize a consensus document on criteria to guide the choice of an ASM for first add-on use. The Delphi Panel agreed that the primary goal of combination therapy is to improve quality of life, that achieving this goal requires optimizing efficacy and tolerability, and that an effort should be made to use a simple treatment regimen. There was also consensus that in patients without seizure freedom, treatment should be aimed at controlling the most hazardous and disabling seizures, such as tonic-clonic seizures and drop attacks [17]. Shortening of the postictal recovery period could also attenuate disability by allowing patients to resume normal functioning sooner after a seizure.

Some of the criteria endorsed by the Panel for selecting a medication for first add-on use are equally applicable to the choice of a medication for initial treatment [18]. This includes selection of an ASM that is effective against the individual's seizure type(s) and unlikely to precipitate other seizure types, and preference of a broad-spectrum medication whenever there is uncertainty about the classification of epileptic events. Other consensus statements equally apply to initial treatment as well as add-on use include the need to consider potential adverse effects, the impact of the ASM on any associated comorbidity, and a drug's ease of use, especially in relation to feasibility of a simple and relatively fast titration, availability of different formulations (including those permitting alternative routes of administration), and no requirement for intrusive safety monitoring procedures. The importance of ensuring an effective communication between patient and physician, particularly with respect to optimizing adherence, and the need to consider individual characteristics were also emphasized. In particular, availability of data on maternal and fetal safety following exposure during pregnancy was considered to be an important consideration when selecting a medication for females of childbearing potential.

A number of considerations which emerged from the consensus statements are more specifically relevant to first add-on use. In particular, suboptimal adherence to the prescribed treatment regimen is a common occurrence in individuals with epilepsy [19] and an important cause of persisting seizures [20]. Therefore, it was appropriate for the Panel to recommend that in individuals with uncontrolled seizures, the possibility of inadequate adherence to the previously used monotherapy regimen should be excluded prior to adding another medication. Other causes of pseudo-pharmacoresistance, such as diagnostic errors or choice of an incorrect medication, also need to be excluded in this setting [21].

Consideration of potential drug–drug interactions is appropriate at any stage of ASM prescribing but is particularly relevant when choosing a medication for add-on use [10]. Clinically relevant pharmacokinetic interactions involving ASMs result mostly from changes in rate of drug metabolism [22]. Enzyme induction typically results in decreased plasma concentration of the affected drug, leading to reduced therapeutic response. Examples include the reduction in plasma concentrations of lamotrigine after adding carbamazepine, or the reduction in plasma concentrations of contraceptive steroids by several ASMs [8,22,23]. Conversely, enzyme

inhibition results in increased plasma concentration of the affected compound, potentially leading to manifestations of overdosage. Examples include the inhibition of lamotrigine metabolism by valproic acid [8], and the impairment of the clearance of norclobazam, the active metabolite of clobazam, by cannabidiol [24,25]. Clinically important ASM interactions can also occur at the site of action [10,26], examples being the synergistic therapeutic efficacy of the combination of valproic acid of lamotrigine [27], the loss of efficacy of brivaracetam added on to levetiracetam [28,29], and the enhanced risk of neurological adverse effects when using combinations of sodium channel blockers [30]. There was agreement among Panel members that drug–drug interactions need to be carefully considered when selecting an ASM for first add-on use, and that in this situation preference should be given, whenever feasible, to medications with a lower potential for adverse interactions. However, perhaps surprisingly, the proposition that ASMs devoid of enzyme inducing properties should be preferred when otherwise equally appropriate alternative treatments exist was supported by only 79.7% of Panel members, just below the 80% threshold required to reach consensus. This might reflect incomplete awareness among neurologists of the relevance of adverse drug interactions as well iatrogenic disease related to enzyme induction [23,31].

If exception is made for specific epilepsy syndromes manageable by precision medicine [32,33], the mechanism of action of an ASM is not generally a primary consideration when selecting a medication for initial treatment. In the management of patients whose seizures continued despite previous treatments, however, mechanism of action considerations has higher relevance, particularly when combination therapy is applied [10]. The hypothesis that combinations of ASMs acting by different mechanisms lead to improved outcomes compared with combinations of drugs acting by the same mechanism has not been tested in well-designed randomized trials but is supported by an accumulating body of preclinical and clinical data [26,34–37]. For example, in clinical trials that led to the regulatory approval of brivaracetam, no benefit was observed in the relatively small subset of patients in whom brivaracetam was added on to levetiracetam, an observation ascribed to competition at the SV2A binding site, which is the primary molecular target for both drugs [28,29]. In a pooled analysis of placebo-controlled add-on trials of lacosamide in patients with focal seizures, median percent reduction in seizure frequency, particularly at the highest dose tested, was considerably lower, and discontinuation of treatment due to adverse events considerably greater, in patients receiving other sodium channel blocking ASMs compared with those not receiving concomitant sodium channel blockers [30]. Likewise, in a study that assessed outcomes of individuals with focal epilepsy included in a large health claims database in the U.S., patients receiving combinations of ASMs with identical mechanism of action had shorter retention on treatment compared with those receiving combinations of ASMs acting by different mechanisms [38]. Additionally, patients receiving specific ASMs acting by different mechanisms also had lower risk for inpatient admission and emergency department compared with patients receiving drugs sharing the same mechanism of action. In agreement with the lines of evidence summarized above, there was consensus among Delphi Panel members that in a patient who did not respond to an appropriately chosen and used ASM, use of another medication with a different mechanism of action would be desirable.

Review of the 10 statements which failed to achieve consensus (supplementary Tables 1–3) raised no concern about the validity of the core messages discussed above. In fact, only three statements were supported by less than two thirds of Panel members. Of these, one related to the comparative impact of seizures versus adverse drug effects on quality of life, and diverging views on this topic

**Table 1**

Suggested recommendations and considerations for selection of an ASM for first add-on use, based on the Delphi Panel's consensus statements.

- 
- The primary goal of treatment should be achievement of a good health-related quality of life
  - Establish an effective communication with the patient and/or caregiver, and inform them about goals and expected outcome, including potential adverse effects
  - Before adding a medication, exclude the possibility of pseudo-pharmacoresistance
  - When choosing a medication, prioritize efficacy and tolerability considerations
  - Choose an ASM which is expected to protect against the individual's seizure type, and not to precipitate other seizure types
  - If the classification of the epileptic events is uncertain, use preferentially a broad spectrum ASM
  - Tailor treatment choice to the characteristics of the individual, such as clinical history, age, gender, co-morbidities and co-medications, in order to optimize tolerability
  - In patients with a history of immune-mediated adverse drug reactions, use preferentially an ASM unlikely to cause allergic reactions
  - Use preferentially an ASM with a mechanism of action different from that of the underlying medication and, possibly, with evidence of favorable synergism
  - If equally valuable alternatives exist, use preferentially ASMs with lower potential for adverse drug interactions
  - Desirable features for an ASM include feasibility of a simple titration scheme permitting achievement of the maintenance dose relatively rapidly; feasibility of once daily dosing; no need for intrusive safety monitoring tests; availability of liquid and solid dosage forms, including forms that permit different routes of administration
  - Take appropriate measures to optimize adherence. This includes informing carefully patients about the goal and implications of treatment, using a simple treatment regimen and ensuring access to plasma drug level monitoring when feasible
  - If seizure freedom cannot be achieved, aim at preventing those seizures that are most hazardous or disabling. Plan appropriate measures to assess clinical response
- 

may be due to differences in treatment practices and perceptions of Panel participants. The two other least supported statements related to whether reluctance to take medications in a public setting affects adherence, and whether it is advantageous for an ASM to possess a selective mode of action. There is little evidence to support either of these statements, which may explain their failure to achieve consensus.

## 5. Conclusions

Selecting an ASM for use as first add-on requires consideration of a wide range of factors related to the individual patient, as well as medication-related factors. This was broadly acknowledged by the present consensus document. The key statements included in the document can be condensed in a list of recommendations, which are summarized in Table 1. Delphi Panel members highlighted in particular the importance of efficacy and safety considerations, adherence issues, the need to take into account individual characteristics, and the specific medication-related properties which should be considered in treatment selection. Most of the criteria proposed to optimize selection of a first add-on ASM also apply to choose a medication for initial treatment. However, there are also criteria which are especially relevant to first add-on use. Among those, the most significant include the need to take into consideration pharmacokinetic and pharmacodynamics interaction between ASMs, and the recommendation to use preferentially combinations of medications with different mechanisms of action.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Antonio Gambardella received speaker's or consultancy fees from Eisai, UCB Pharma and Zogenix. Paolo Tinuper received speaker's or consultancy fees from Arvelle, Eisai, GW Pharma, LivaNova, UCB Pharma, Xenon Pharma and Zogenix. Benedetto Acone received speaker's or consultancy fees for projects sponsored by Eisai, Astra Zeneca, Novartis, Gilead, Abbvie, Sanofi, Sandoz, Sobi, MSD, Angelini, AlfaSigma, Janssen, Kyowa Kirin, Abiogen, Amgen, Teva; Giangennaro Coppola received speaker's or consultant fees from Eisai and Humana; Paolo Bonanni received speaker's or consultancy fees from Eisai, LivaNova, Lusofarmaco and Proveca; Emio Perucca received speaker's or consultancy fees from Arvelle, Biogen, Corlieve, Eisai, GW Pharma, Sanofi, Sun Pharma, UCB Pharma, Xenon Pharma and Zogenix.

## Acknowledgments

This project was made possible by non-conditional financial support provided by Eisai S.r.l., Milan Italy.

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## Appendix B. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.yebeh.2021.108087>.

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