Identifying key unmet needs and value drivers in the treatment of focal-onset seizures (FOS) in patients with drug-resistant epilepsy (DRE) in Spain through Multi-Criteria Decision Analysis (MCDA)

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ABSTRACT

Introduction: Epilepsy is a serious neurological disease, ranking high in the top causes of disability. Approximately 40% of patients with epilepsy are pharmacoresistant after their seizures failed at least two antiseizure medications (ASMs). Adult patients experiencing focal-onset seizures (FOS) account for approximately 60% of all patients with epilepsy and they are more likely to become drug-resistant epilepsy (DRE) than those with generalized onset. Drug-resistant epilepsy is associated with mortality, morbidity, and reduced quality of life. The information available on the clinical management, health outcomes, and unmet needs of the disease within the Spanish healthcare environment is very limited. Multi-Criteria Decision Analysis (MCDA) allows determination of what represents value in a given indication considering all relevant criteria for healthcare decision-making in a transparent and systematic manner and from the perspective of relevant stakeholders.

Purpose: The aim of this study was to identify the burden of DRE (clinical, quality of life, and economic) and the unmet needs in Spain and to determine what represents value in the treatment of FOS in DRE patients from the perspective of Spanish epileptologists.

Methods: The steps taken to carry out the MCDA were based on previously published good methodological practices. A systematic literature review (combining biomedical databases and gray literature sources) was performed between March and April 2020. Results were reviewed and validated with three epileptologists in June 2020 and used to develop a MCDA value framework, adapted for FOS in DRE, composed of 12 quantitative criteria and 3 contextual criteria. A group of six Spanish epileptologists from four Spanish regions were trained in MCDA methodology before individually validating value criteria (and their definitions based on literature review findings) and assigned relative weights using an ordinal 6-points scale. Results were analyzed and discussed in a group meeting through reflective MCDA discussion methodology.

Results: Drug-resistant epilepsy is considered a very severe health problem with important unmet needs affecting a considerably sized population. While safety and impact on quality of life of available ASMs are considered adequate, efficacy remains insufficient for patients to achieve seizure freedom and maintain it over time. Hence, the therapeutic benefit of pharmacological treatments currently used is regarded as suboptimal. Drug-resistant epilepsy management is associated with moderate pharmacological, relevant direct medical and high indirect costs. Quality of evidence available for current treatments is moderate. It is considered that DRE does not currently stand as a key priority for the Spanish healthcare system.

Abbreviations: ASMs, Antiseizure medications; DRE, Drug-resistant epilepsy; EVIDEM, Evidence and Value: Impact on Decision Making; FOS, Focal-Onset Seizure; HRQOL, Health-related quality of life; ILAE, International League Against Epilepsy; MCDA, Multi-Criteria Decision Analysis; RCT, Randomized Clinical Trial; PROs, Patient-Reported Outcomes; PWE, People with Epilepsy.

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1. Introduction

Epilepsy is one of the most common brain conditions affecting approximately 50 million people worldwide [1] and about 400,000 patients in Spain [2,3]. It is characterized by a lasting predisposition to generate spontaneous epileptic seizures and has numerous neurobiological, cognitive, and psychosocial consequences [4]. Focal-onset seizures (FOS) occur in more than 60% of people with epilepsy (PWE) and are the most commonly encountered type of seizures in the adult population [2].

For most PWE, antiseizure medications (ASMs) are the main treatment modality [5], with the aim of achieving seizure freedom without causing side effects which can affect quality of life. Despite the approval and availability of more than 20 different ASMs for the treatment of epilepsy, with many different efficacy and safety profiles, approximately 40% of patients, particularly those with focal seizures, present drug-resistant epilepsy (DRE) [6]. The International League Against Epilepsy (ILAE) defines DRE as treatment failure to two tolerated, appropriately chosen and used ASM schedules (in monotherapy or in combination) to achieve sustained seizure freedom for twelve months or three times the preintervention interseizure interval, whichever is longer [7].

Based on the clinical practice guidelines of the Spanish Society of Neurology (2019), there is no specific protocol for the use of ASMs in DRE, and treatment choice should be individualized according to the patient’s profile [8]. Additionally, the information available on the clinical management and unmet needs of the disease within the Spanish healthcare environment is very limited [2,8].

Reflective Multi-Criteria Decision Analysis (MCDA) offers a methodology and framework that allows determination of what represents value in a given indication considering all relevant criteria for healthcare decision-making in a transparent and systematic manner and from the perspective of relevant stakeholders [9,10].

Reflective MCDA methodology has already helped elicit the views of different stakeholders [11] during evaluation and decision-making relative to the use of orphan drugs [12-14], immunotherapy in cancer [15], chronic inflammatory skin diseases [16], pulmonary arterial hypertension [17], prostate cancer [18], and thyroid cancer [19] among others. Multi-Criteria Decision Analysis methodology is already being used in Spain to assess the value contribution of new treatments at regional [12,20] and hospital levels [21].

The EVIDEM (Evidence and Value: Impact on Decisison Making) 4.0 framework is a standardized reflective multi-criteria framework focused on the context in which healthcare decisions are made. This framework, based on ethical principles, was specifically designed to evaluate healthcare interventions and to facilitate decision making [22].

This study was focused on the determination of current burden (clinical, economic and social), unmet needs and key value drivers for DRE patients with FOS using MCDA methodology from the perspective of Spanish epileptologists.

2. Methods

2.1. Study design

The study was designed according to MCDA methodology [9,10] steps: literature review, evidence matrix development, criteria scoring, aggregate scoring, value determination, and discussion of the findings. An EVIDEM MCDA framework [22] was used and specifically adapted to determine what represents value in the management of FOS in adult patients with DRE in Spain.

2.2. Literature review

A systematic literature review [23,24] was conducted between March and April 2020 to obtain relevant information on the disease and its current management in Spain. The literature review was carried out according to a protocol including the criteria of the adapted EVIDEM MCDA framework. All articles identified through the search were screened by title and abstract. Articles not responding to the search objective or not meeting eligibility criteria were excluded. A full-text assessment was performed with those remaining. Articles not containing the elements required by the aims and objectives of the study were excluded and those remaining were included in the study and thoroughly analyzed.

Published evidence was searched using biomedical databases: MEDLINE [25], Cochrane [26] and MEDES [27] (Spanish database). The search included published articles in English or Spanish. It was complemented using gray literature sources such as Google Scholar, patient associations’ websites, and available documents from official sources (e.g., European Medicines Agency (EMA), Spanish Medicines Agency (AEMPAS), and Spanish regional and hospital evaluations).

2.3. Reflective MCDA tool and evidence matrix development

The EVIDEM MCDA framework (version 4.0) [22] was used as a starting point for the study. This framework is composed of a total of 20 criteria structured into two distinct sections: MCDA Core Model (composed of 13 quantitative criteria focused on product evaluation) and the MCDA Contextual Tool (composed of 7 contextual criteria focused on the consideration of the context surrounding decision-making).

Since the study focused on assessing a healthcare problem and not on the evaluation of the relative value contribution of a given treatment, selection and structuring of quantitative criteria (MCDA Core Model) (excluding the comparative criteria) and qualitative criteria (Contextual Tool) was performed. Hence, the adapted MCDA-value framework is composed of a total of 15 criteria (12...
2.4. Expert panel design and conduct of the study

An expert panel of 6 clinicians involved in the management of epilepsy treatments from four Spanish regions (Andalucía, Cataluña, Madrid, and Comunidad Valenciana) were invited to participate in this study. Members were selected based on their expertise, while trying to achieve a balanced geographical representation. A qualitative study was carried out with a staged approach. The first step was an online meeting (held on June 10th, 2020) in which participants received basic training on reflective MCDA methodology. The MCDA value framework adapted to DRE was presented to study participants for group review, discussion, and validation. The second step involved individual, remote scoring of the framework value criteria and reflection of rationale behind each criterion scoring (finalized by June 24th, 2020). A direct rating scale was used in which each participant gave a score per criterion using a simple 6-point scale (0 = lowest value, 5 = highest value). The third, final step, which took place on June 30th, 2020 consisted in an online collective discussion of scoring results and reflections behind individual scores.

2.5. Data analysis

Data were collected individually from each participant, transferred to a common database and analyzed using Microsoft Excel software. Scores were analyzed quantitatively. Results were calculated and shown to study participants in the form of mean, standard deviation (SD), and range of minimum and maximum scores. Comments and reflections behind experts' scores were analyzed and discussed in a qualitative manner.

3. Results

3.1. Literature review

A total of 119 publications from biomedical databases (n = 75) and gray literature (n = 44) were identified and from these, a total number of 87 publications were finally selected and included. All other publications (n = 32) were excluded based on title, abstract and/or full-text screening.

The MCDA value framework was populated with data from the total of 87 identified references (Fig. 1), found in biomedical databases (n = 43), available documents from official sources (e.g. EMA, AEMPS) (n = 5), regional and hospital evaluations (n = 7), clinical guidelines or protocols (n = 10), and online gray literature (n = 22).

The number of references selected/discarded at each decision point was recorded and is represented on a PRISMA flow diagram [28].

3.2. Performance scores based on evidence and participants’ insights

According to the results collected from the individual scoring (range 0–5; see methods section) by study participants (Fig. 2), “Disease Severity” received a score of 4 ± 0.6 (mean score ± SD) reflecting experts’ perception of its impact on mortality, morbidity, and patient’s and caregivers’ quality of life. All participants assigned a high score value to this criterion being one with the greatest consensus. “Size of affected population” scored 3.3 ± 0.8 based on prevalence and incidence of DRE in Spain and with differences in perception among participants. The “Unmet needs” criterion scored 4.2 ± 0.8, as all participants agreed that DRE is a condition with important unmet needs, mainly with regard to the need for more effective ASMs with the potential to change the natural history of epilepsy and the need for earlier, adequate diagnosis which could improve the management of DRE. It was pointed out that, in clinical practice, there is inequity in availability of resources to treat DRE patients across Spanish hospitals and regions (e.g., regarding Video-EEG evaluation, frequency of medical visits, and expertise of healthcare professionals).

“Efficacy and effectiveness” of available ASMs scored 2.3 ± 1. Although it was agreed that the main unmet need in terms of efficacy focuses on achieving seizure freedom, there were differences in perceptions related to other achieved outcomes assessed in randomized clinical trials (RCTs) such as responder rates and percentage change in seizure frequency. Moreover, although there are ASMs which are being used for DRE in clinical practice, currently none of them have the specific indication for the treatment of DRE and their choice depends on the individual clinical history of each patient since no specific protocol for this condition is available.

“Safety and tolerability” was scored with 3.7 ± 1. The important dispersion rate in scoring results was discussed. Overall, the safety and tolerability profiles of current ASMs are considered acceptable. Although some epileptologists consider that the need to treat patients with a combination of several ASMs with the subsequent increase in overall drug load results in poor safety and tolerability.

“Patient-Reported Outcomes (PROs)” were assessed with a score of 3.7 ± 0.8 as a result of a perceived balance between efficacy and safety of available treatments by participants which results in a preserved quality of life for patients.

The “therapeutic benefit” of available pharmacological treatments is considered modest (score of 2.3 ± 0.8) as current outcomes with ASMs are regarded as suboptimal providing only symptomatic benefit and not impacting the course of the disease, since they are limited to reducing the number of seizures and seizure freedom is not achieved in a significant proportion of patients.

“Cost of intervention” scored 2.8 ± 0.8 in terms of pharmacological cost. It is considered that the cost of ASMs is relatively low when compared to the overall costs associated with epilepsy. The “other medical costs” criterion received a high score of 3.3 ± 1.4, taking into account associated hospitalizations, visits to emergency units, medical visits, and outpatient procedures. “Non-medical cost” scored 3.8 ± 1.2, based on the big financial burden on patients, their families, and caregivers, derived from associated lack of productivity, cognitive dysfunction, unemployment, and early retirement. It was discussed that, overall, cost of treatment of DRE could be considered moderate, although is relatively low when compared to other neurological diseases (e.g., multiple scler-

| Quantitative criteria | Disease severity | Unmet needs | Size of affected population | Efficacy/Effectiveness | Safety/Tolerability | Patient-reported outcomes (PROs) | Type of therapeutic benefit | Cost of intervention | Other medical costs | Non-medical (indirect) costs | Quality of evidence | Clinical Practice Guidelines |

| Contextual criteria | Mandate and scope of healthcare system and population priorities and access | Common goal and specific interests | System capacity and appropriate use of intervention |

Table 1

Criteria included in the adapted EVIDEM MCDA framework for the assessment of focal-onset seizures in patients with drug-resistant epilepsy in Spain.
rosis) [29]; that is why the above-mentioned economic criteria present a high dispersion rate due to differences in perceptions.

“Quality of evidence” supporting currently used pharmacological treatments received a score of $3 \pm 1.8$. Despite the divergence in opinions, as shown by the high dispersion rate (0–5), it is considered that the design of RCTs of available ASMs present several limitations including, among others, not having included seizure freedom as a primary endpoint.

The “clinical practice guidelines” (CPG) criterion scored $3.5 \pm 1.9$ and presented a significant dispersion rate (0–5). It is considered that, despite the availability of several CPG at the national [8] and regional [30–32] levels in Spain, these do not provide clear guidance for treatment of DRE and application of recommendations require experience and adaptation to each clinical and personal circumstance. Hence, expert opinion still represents the best option to date.

With regard to qualitative criteria, “mandate and scope of the healthcare system and population priorities and access” was assigned a low score ($1.5 \pm 1.4$). It is considered that DRE does not stand as a key priority for the Spanish healthcare system, not being reflected within the objectives of national strategies, although it is included in the regional healthcare plan of the Community of Valencia [33]. The “Common goal and specific interests” criterion scored $4.2 \pm 0.8$. It was agreed that ensuring an adequate treatment and management of DRE is aligned with the common goals and key objectives from Spanish relevant scientific societies and patient associations. The criterion “system capacity and appropriate use of intervention” was scored with $3.8 \pm 1$. It is believed
that the Spanish healthcare system has capacity to address the health problem and it is ready for the introduction of new pharmacological alternatives for the treatment of FOS in patients with DRE.

In summary, according to the results collected from the individual scoring by study participants (Fig. 3), the highest scores were assigned to “unmet needs” (4.2 ± 0.8), “common goal and specific interests” (4.2 ± 0.8), “disease severity” (4 ± 0.6), “non-medical costs” (3.8 ± 1.2), and “system capacity and appropriate use of intervention” (3.8 ± 1). The criteria with lowest scores were “mandate and scope of healthcare system and population priorities and access” (1.5 ± 1.4), “efficacy/effectiveness” (2.3 ± 1), “type of therapeutic benefit” (2.3 ± 0.8) and “cost of intervention” (2.8 ± 0.8).

4. Discussion

The current study focussed on FOS, since it represents the majority of DRE [2]. The concept of what represents value in drug-resistant FOS and what are the key unmet needs in Spain can vary among healthcare professionals, resulting in a range of definitions. Multi-Criteria Decision Analysis facilitates decision making by explicitly addressing each factor, assigning it a score. The criteria identified as the most important in this study are fully aligned with key publications on the current situation of DRE management in Spain [8,34,35].

Drug-resistant epilepsy is considered a severe condition which affects the quality of life of patients and their caregivers and it is associated with a higher risk of mortality compared to the general population [2].

Through the study methodology, experts identified several, important “unmet needs” including the insufficient number of referrals to specialized epilepsy units that leads to misdiagnosis, late detection, and delayed instauration of effective therapies [35]. Although the Spanish Ministry of Health has granted access to the evaluation of patients through reference centers focusing on DRE, access to them represents a problem for many patients and is highly dependent on decisions by referring physicians and availability of resources at regional level [36]. Another identified key unmet need referred to the lack of effective pharmacological treatments. This perception is in line with the results of a study showing that, despite the introduction of new ASMs in the last decade, with acceptable safety and tolerability profiles, the response to pharmacological treatment has not been substantially modified compared to previous years [6,37].

Given the lack of reliable epidemiological data and the above-mentioned infra-diagnosis rates, the estimation of the total Spanish population affected by DRE is challenging as diagnosis is problematic and its specific definition is not always easy to apply to specific patients. Epileptologists recognized DRE according to the definition of the ILAE [7] following recommendation of the CPG of the Spanish Society of Neurology (2019) [8]. Nevertheless, the individual patient status of DRE can change over time. Therefore, it might be advisable to provide unlimited access to specialized epilepsy care and continue making therapeutic efforts in these patients.

High importance has also been assigned to the impact on the quality of life of PWE and their caregivers. Emotional distress, social isolation and stigmatization, dependence on family, poor employment opportunities, and personal injury add to the suffering of PWE [38,39]. A number of studies, including data from Spain, have demonstrated the negative impact of DRE in patients’ health-related quality of life (HRQOL) [40-43]. Its association with high unemployment rates and occupational incapacity has also been reported [41,44,45]. More than one-third of patients need a caregiver for day life activities [44] and caregivers’ quality of life is also negatively impacted both physically and mentally [46].

The costs associated with the treatment of DRE has also been identified as a key value criterion and burden driver in this study. This is in line with publications indicating that DRE consumes a high percentage of healthcare resources, with a considerable cost for the Spanish National Healthcare System, impacting both primary and specialized care [41,47]. Drug-resistant epilepsy also results in a considerable budgetary impact for patients and their families/caregivers [44], particularly in rural and remote regions where equity of access to necessary resources and skilled medical care can be difficult [34,35].

Adequate reflection of management and treatment of DRE in clinical practice guidelines/consensus documents has also been identified as a key value driver. However, at present, and despite the availability of general epilepsy guidelines [8,30,32], no specific clinical guidelines for DRE are available in Spain.

The scores obtained using the suggested MCDA framework are intended to inform a debate and highlight which criteria are of greater value when evaluating and making a decision on a treatment for FOS in patients with DRE. It also aids elucidation of the relative positioning of treatment alternatives in clinical practice by allowing epileptologists to study the specific patient’s case and assess which drug would be most valuable in that context.
on the basis of the MCDA framework’s quantitative results. For example, a treatment that modestly reduces seizure frequency may not be regarded as valuable unless it also provides high safety and tolerability. In addition, MCDA methodology can improve stakeholder participation and facilitate conflict mediation. Rethinking how value is defined for a given indication could also play an important role in driving future drug development.

Spanish evaluators and decision makers have already considered the use of MCDA frameworks (and their value criteria) as a complete and useful tool, feasible to be used for drug evaluation and decision-making in Spain [12,48]. In recent years, there has been increased interest in MCDA, and studies reflecting its use in Spain and elsewhere have highlighted its usefulness in providing a list of criteria to objectively and transparently determine what represents value and to evaluate the use of a drug in a given indication.

Our study has supported that MCDA can be a successful tool to assess a health problem such as FOS in patients with DRE and for determining the current associated burden and key unmet needs in its management and treatment in Spain. Here, we have proposed a standardized MCDA framework with a set of 15 criteria to aid epileptologists to assess drug value contribution in treatment of FOS in patients with DRE.

This study has several strengths. First, using the EVIDEM MCDA methodology, each criterion was evaluated transparently and objectively, also providing and considering a contextual tool for analysis, relevant to where decision-making takes place. Second, study participants were trained in criteria scoring and analysis to ensure correct understanding of the methodology and objective analysis. Scoring criteria enabled a reflective discussion and clarified definitions and interpretations within the expert group.

The experts participating in the study were selected based on their clinical practice experience, number of relevant scientific publications in the field and their membership to epilepsy expert centers in Spain.

However, the study is not exempt from some limitations. First is the limited number of experts participating in the study. The reason for choosing a relatively small panel size in MCDA exercises facilitates participation in group discussions and sharing of perspectives, allowing a more in-depth analysis of the different value criteria assessed. Although the number of experts involved in this study is in accordance with those from previous, similar MCDA studies [16,19,49] and resembling the number of experts who form part of evaluation committees in Spain, additional future work, with a larger group of experts, could be warranted to validate study findings.

Second, this study only considers the perspective of physician experts in DRE. However, it could be interesting to expand this study to include other figures (e.g., patients, evaluators, decision-makers) to include different perspectives from key stakeholders involved in DRE in Spain.

Third, and as for other MCDA studies performed in Spain, the information presented in the value framework was limited by the information and data publicly available at the time of the study. Therefore, results might change when new data become available, warranting a follow-up to this study.

5. Conclusions

Drug-resistant epilepsy is considered a severe health problem, associated with increased mortality, morbidity, and reduced HRQOL for patients and their caregivers. It is associated with high unmet needs, especially regarding the availability of treatment alternatives that provide added efficacy over existing therapeutic alternatives.

Reflective MCDA has been proven to be a useful tool to carry out a systematic, transparent, and robust procedure to assess the value of treatment and management of FOS in patients with DRE. It allowed the determination of key clinical, economic, and humanistic drivers of DRE-associated burden, identifying current key unmet needs in a holistic way and from the point of view of experts in Spain in DRE.

It is expected that, as for other therapeutic areas, the MCDA methodology used in this study will be used in a near future for informed decision-making in the epilepsy area by pharmacotherapeutic commissions at the regional and hospital levels in Spain, contributing to respond to some of the identified unmet needs, to the management and treatment of patients suffering from DRE, and for the development and advancement of relevant healthcare and pharmaceutical policies.

To our knowledge, this represents the first study to determine what represents value of treatment and management of FOS in patients with DRE using reflective MCDA methodology in Spain.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Villanueva has participated in advisory boards and industry-sponsored symposia by Arvelle, Bial, Eisai Inc, Esteve, GW Pharmaceuticals, Novartis, Sandoz, UCB Pharma and Zogenix. Dr. Carreño has received honoraria for advisory boards/consultancy from Arvelle, Bial, Eisai Inc, GW Pharmaceuticals, Sanofi and UCB Pharma; speaking fees from Bial, Eisai, Sanofi and UCB Pharma; and research grants from Eisai Inc. Dr. Gil-Nagel reports receiving research grants, or honoraria from speakers or advisory boards from Arvelle, Bial, Biocodex, Eisai Inc, Esteve, GW Pharmaceuticals, Stoke, UCB Pharma and Zogenex. Dr. Serrano-Castro has received honoraria or served as a paid consultant for Arvelle, BIAL, Eisai Inc, GW Pharmaceuticals, Novartis and UCB Pharma. No other potential conflicts of interest are reported. Dr. Serratosa has received research grants or honoraria as speaker or participant in advisory boards from Arvelle, BIAL, Eisai Inc, Esteve, GW Pharmaceuticals, Sanofi, UCB Pharma for participation in advisory boards or pharmaceutical industry-sponsored symposia. Dr. Toledo has participated in DRE clinical trials with different ASMs development and reports receiving consulting fees from Arvelle, Bial, Eisai Inc, GSK, GW Pharmaceuticals and UCB Pharma.

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