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Selecting anti-epileptic drugs: a pediatric epileptologist's view, a computer's view

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Abstract

Objective—To identify which clinical characteristics are important to include in clinical decision support systems developed for Antiepileptic Drug (AEDs) selection.

Methods—Twenty-three epileptologists from the Childhood Absence Epilepsy network completed a survey related to AED selection. Using cluster analysis their responses were classified into subject matter groups and weighted for importance.

Results—Five distinct subject matter groups were identified and their relative weighting for importance were determined: disease characteristics (weight 4.8 ± 0.049), drug toxicities (3.82 ± 0.098), medical history (3.12 ± 0.102), systemic characteristics (2.57 ± 0.048) and genetic characteristics (1.08 ± 0.046).

Conclusion—Research about prescribing patterns exists but research on how such data can be used to train advanced technology is novel. As machine learning algorithms becomes more and more prevalent in clinical decisions support systems, developing methods for determining which data should be part of those algorithms is equally important.

Keywords

epilepsy; pediatric neurology; decision support; anti-epileptic drug selection; artificial intelligence

Introduction

Healthcare data are ubiquitous and complex. In some cases, like the Mock Turtle's Calculator in *Alice in Wonderland* (1), they unintentionally distract. The Institute of Medicine explains the problem thus: 'Professional judgment will always be vital to shaping care, [but] the amount of information required for any given decision is moving beyond unassisted human capacity' (2). This study addresses how to select and validate the data that are important when prescribing anti-epileptic drugs (AEDs). Research about prescribing patterns exists (3), but research on how such data can be used to train advanced technology is novel.

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Conflict of Interest

The authors have no conflicts of interest.

AED selection

Childhood absence epilepsy (CAE) is the single most common form of childhood epilepsy for those between 4 and 8 years of age (4, 5). It is characterized by very frequent daily absence seizures in an otherwise normal child. By the age of 16, the cumulative risk of epilepsy approaches 1% (6, 7), which means that CAE will occur in 0.1% to 0.17% of children. The EEG for these patients usually demonstrates a 3-Hz generalized spike-wave pattern with normal background activity (8–10). Because those features make CAE easily recognizable, diagnosis can be made with excellent inter-rater reliability (4).

CAE treatment is primarily pharmacological, with the aim of eliminating or reducing the seizure frequency without harm from the drug's side effects or the epilepsy itself. Selecting drugs to achieve that has been hampered by the gaps in knowledge about the best initial therapy. It was not until 2006 that the International League Against Epilepsy (ILAE) published evidence-based guidelines for monotherapy (11). Until then, drug selection for CAE had been guided by the results of underpowered clinical trials (12–17). The ILAE guideline emphasized other factors (e.g. genetic and environmental) could impact drug selection. Recently clinicians have begun favoring clinical decision support systems to help them integrate all the relevant factors when making a treatment decision (18).

The clinical decision support system

Clinicians are under intense pressure to make high-quality decisions for an ever-increasing array of ailments. The pressure is exacerbated by a deluge of information that may or may not be helpful. Because of the sheer volume of data and its sometimes dubious quality, clinicians often rely on what they learned during training or from over-interpreted clinical experiences (19, 20). Even though the emergence of the CDSS provides some relief in managing the deluge of data, some hesitancy about adopting it arises because clinicians view such systems as incomplete or complex (21). Their hesitancy diminishes, however, when they experience the ease of CDSS use, its integration into the clinical workflow, and its evidence-based recommendations (22).

The design of a CDSS must respect the end users' needs. A well-designed CDSS should focus clinicians, not distract them. It should be adept at culling through and organizing the avalanche of biomedical data by using advanced text-mining algorithms. It should present information in a way responsive to the end users' profiles. It should catalyze decision making not attenuate it (23). A CDSS need not be complex; it should be designed to fulfill its stated aim and be free of superfluous information. A CDSS for dose-range checking is elegant in its simplicity. A CDSS for disease-specific therapy identification will indeed have an underlying complexity because of the relationships among patient, diagnosis, and environment, but the complexity should be transparent to the user.

The many different aspects by which to classify CDSS cluster into five general features (24–28):

- *feedback* – they provide feedback by responding to an action taken by the clinician or to new data entered into the system.
- *proactive information* – they present information at the point of need.
- *intelligent action* – they automate routine tasks.
- *communication* – they provide various alerts.
- *expertise* – they use various computational methods for combing through extensive data to provide diagnostic and therapeutic information.

Expert system

This research report focuses on the last characteristic listed: expertise. An expert system is a software that attempts to answer a question, to provide domain-specific information or to provide clarity when more than one human expert should be consulted. Of the wide variety of present methods for developing an expert system, most require (29):

- *a knowledge base* that has captured the expertise of a subject matter expert.
- *a process* for gathering the knowledge.
- *a process* for placing the expert system in a real-world situation.
- *a process* for evaluating the performance of the system.

The aim of this research is to identify the features that pediatric epileptologists use when selecting an anti-epileptic drug (AED). The results will seed the knowledge base used in The Children's Hospital Resource In Selecting Therapy Individualized Expert (CHRISTINE) for AED selection (30). The focus is on two aspects of the CHRISTINE system:

- *adjustment* of the weighting scale used in a drug selection recommendation score.
- *reduction* in the features that comprise a drug selection recommendation score.

The knowledge base is essential to an expert system; in fact, an expert system can do nothing until the relevant data exist in a format usable by computers. That formulation is the task of a knowledge engineer. Knowledge engineering is an engineering discipline that systematically integrates knowledge into a computer system so that complex problems that normally require a high level of human expertise can be solved numerically (31). In general, knowledge engineering includes assessment, development of a knowledge structure, acquisition of information, testing and validation of information, integration of information into a computer system, and revision and evaluation. Our previous work described how CHRISTINE's knowledge base is designed (30). Here, we explain how the AED knowledge base was developed using expert opinion, and how it is used in the CDSS using cluster analysis.

The Children's Hospital Resource In Selecting Therapy Individualized Expert

Figure 1 shows the components of CHRISTINE and how they collaborate to provide clinical decision support. At its core, CHRISTINE is a CDSS framework that provides an environment for developing and implementing different expert systems.

Each module within the CHRISTINE framework defines one expert system. So far, separate expert systems for epilepsy, Attention deficit hyperactivity disorder, mood disorders, neuropsychological, end-of-life, and suicide assessments have been or are being developed. CHRISTINE is built using open source software that ensures it can be distributed without licensing fees. The development is done with a combination of Perl, MySQL, HTML, JavaScript, Bash, and Java, making a highly extensible web application. While all expert systems share CHRISTINE's common framework, each one contains its own domain-specific configurable knowledge base, for example, for epilepsy, a set of configuration files defining the data collection process and a set of rules for calculating drug selection recommendation score. Support for CHRISTINE was provided by a private donation.

The initial knowledge base for the AED expert system included 22 features (Tables 2 and 3), for example, *drug efficacy*, *laboratory findings*. The 22 features comprise 701 individual factors that affect the recommendation score. The high number of individual factors results from the fact that they combine a total of 294 variables. For example, the feature *drug efficacy* would contain factors that combine three variables: *seizure typeage group*, and

either *monotherapy* or *adjunctive therapy* type, for example, *absence seizure*, *adolescent*, and *adjunctive therapy*. Because the variables consist of drug–drug interactions, not all 294 variables are collected for every patient. The variables are context sensitive. On average, a total of 90 drop-down or radio button–type questions are answered per patient. Each feature and each factor has its own value in the system. The drug recommendation score is simply a summation of all factors that apply to a patient, scaled by feature weights. This process creates a complex but transparent system. The purpose of this research is to determine whether some of the features of the CDSS can be reduced and how to scale the feature weights.

Methods

Methods included initial content development, content validation, expert ranking, and ranking by cluster analysis.

Initial content development

The seminal decision criteria for CHRISTINE's knowledge base were compiled by a pediatric epileptologist. The list was based on 25 years of clinical experience and a literature review (11). The list of 22 items is shown in Tables 2 and 3 in the column labeled 'Initial Features', along with a number of factors associated with each feature.

Content validation

The seminal criteria were then reviewed by three additional pediatric epileptologists. The items from the initial list were combined with the validated version to yield the 30-item list as shown in Tables 2 and 3 in the column labeled 'Revised Features.' It is this list of features that was used for the surveying, ranking, and selection needed by the computational algorithms to support drug selection.

Expert ranking

Each feature shown in column two of Tables 2 and 3 was printed on three separate pages of a survey, one page for infants between 1 and 24 months of age, one page for 2- to 12-year-olds, and one page for patients over 12 years of age. Members of the United States National Institutes of Health (NIH) Childhood Absence Epilepsy network were asked to respond to the following statement: 'Consider the last 50 patients for whom you personally had to make an AED decision in this age group. Do not worry about whether you were treating someone using AED monotherapy or polytherapy, just think about your last 50 patients in that age group where an AED decision was made. Please rank how often each of the features impacted your AED decision-making process. Use 5 for 'always impacted the decision' and 0 for 'never impacted the decision'. The averaged results of these responses are shown in Table 4.

Cluster analysis

Cluster analysis comprises mathematical algorithms that group similar data. Here it is used to find natural groupings of drug selection criteria. If such groupings exist, they could identify the ranking and provide a cut-off point for drug selection features. To cluster the expert opinions, a data matrix was prepared containing the responses to each question by age group. Missing values were replaced with the average value for Selecting anti-epileptic drugs that question. Then, an average response across all age groups for each respondent was calculated. That yielded a matrix of 23 columns (respondents) and 30 rows (features). The Euclidean distance between rows (features) was then calculated to produce a distance

matrix that was used to compute a hierarchical tree using a hierarchical minimum variance linkage algorithm (Ward's method).

Basically, at each step, the union of every possible cluster pair was considered and the two clusters that have the least variability were combined. This process was iterated until there were no pairs left. The result is a hierarchical structure showing responses with similar answer patterns in the same leaf nodes (32). Next, the most stable clusters were selected. To do that, we used a common method called the leave-one-out sampling procedure (33–37). Using this approach, the clustering procedure was repeated once for each respondent (23). Each time, an expert's response was excluded. Let's say we set the number of clusters to be k . For each k , a cross-classification table with 23 and 253 unique pairs of data groupings is created. If k produces stable clusters, then each pair should agree with each other. This level of agreement can be measured by a corrected Rand index (34, 36). The most stable clusters are generated by a k that maximizes the average agreement between different pairs (Fig. 2).

Results

The respondents' demographics, listed in Table 1, show that 23 epileptologists, all members of the NIH Childhood Absence Epilepsy network, completed the survey. On average, they had graduated from medical school 24.5 (SD=8.6) years ago, and seventy percent were men. The decision criteria are divided into two tables: drug criteria are shown in Table 2, and patient criteria are shown in Table 3. Each table has two columns. Column one, 'Initial Features', shows the seminal decision criteria and a number of factors associated with this feature. The second column, 'Revised Features', shows the criteria that were ultimately selected through the content validation process and used in the expert survey. The results of the survey by mean score and by age are shown in Table 4. This table also shows that a cluster label was assigned most often and its frequency during the leave-one-out procedure.

The revision of the initial feature list by three additional local epileptologists (Tables 2 and 3) led to the removal of two features from the seed list (*drug-related mutagenic effect* and *patient pubertal status*) and to six features being subdivided (*drug practical issues*, *drug efficacy*, *drug effect on patient co-morbidities*, *drug-drug interactions*, *patient demographics*, *non-genetic disease-related laboratory findings*, and *non-genetic, non-disease-related laboratory findings*).

Figure 2 shows that five clusters are needed for maximum stability. This means that even if we eliminate an expert's responses, the remaining features found in a cluster will be roughly the same. Table 4 shows how often a feature was assigned to a particular cluster for all 23 runs of the algorithm. The results show that cluster 3 is the least stable, with the instability caused primarily by the '*cost of the drug*' feature, which was assigned to cluster 3 only 78% of the time. Naturally, the third cluster has the most internal variation, 0.102 (Table 5). The variance within all clusters is so compact that the differences among all clusters are significant (two sample t-test $P < 0.01$), which is to be expected as the clustering procedure optimizes this criterion (Ward's method).

Table 4 shows that *genetic efficacy*, *race*, *ethnicity*, and *genetic metabolism* are rarely used in the drug selection process. This means that potentially 28 individual factors need revision.

Finally, Table 5 shows that the CDSS scoring system can be greatly simplified. First, it seems that using a five-level system to rank individual factors based on their importance in the drug selection process is sufficient. Today, the system uses 16 ranks, with values between 280 and 0. Second, the 30-features list shown in Tables 2 and 3 can be replaced with a five-item list from Table 5 with very little loss of variability in the system.

Discussion

Pediatric epileptologists currently can choose from over twenty anti-epileptic drugs for several types of seizure and epilepsy. To choose an appropriate AED, the clinician must co-consider numerous patient and drug characteristics. This research defined and validated the selection of the 30 features used in this crucial process for the decision-making process. Through the expert survey, this research also reduced and defined the features in the order of importance according to age group. This expert opinion seeding the AED selection knowledge base was determined by the well-known and proven Delphi method. The Delphi method, also known as collective intelligence, is based on the principle that decisions from a structured group of individuals Selecting anti-epileptic drugs (such as experts in a particular field of medicine) are more accurate than are those from unstructured groups (34, 35). Experts are used because of their large accumulation of background knowledge and their cultivated sensitivity to its relevance that drives their decisions. However, a consensus of experts is needed because individual experts will disagree, making reliance on a single expert problematic (35). The Delphi method includes characteristics that manage anonymity (to avoid dominance), iteration (to allow for changing ones' mind), controlled feedback (showing the group's response), and statistical group response (expressing judgment using summary measures). The Delphi method has been widely used and accepted in such areas as public policy issues, economic trends, health and education forecasting, and business forecasting (34).

Once the AED selection features had been reduced and weighted, knowledge engineering was used to integrate that content into the initial knowledge base to provide a more succinct and sufficient CDSS. Epileptologists are not unique in seeking out methodologies to help them manage the exponential volume of patient data, research, and treatment-specific information that is available in a CDSS. There are numerous examples of CDSS currently being developed and implemented to support clinicians in their decision making (36). Until CDSS arrive at a medical decision, a clinician would often use a more traditional algorithm: a static two-dimensional approach without the capacity to integrate unique patient information, current medical discoveries, and expert opinion. Integrating all this information can generate more appropriate treatment recommendations to aid the clinician in the making a decision.

Our findings suggest that pediatric epileptologists commonly use 30 items, shown in the Revised Features list in Tables 2 and 3, to help with the selection of an AED We showed that these features could further be mathematically organized and classified into five different selection clusters.

The highest weighted selection cluster is the disease characteristics cluster, containing the features EEG, seizure type, and syndrome. Using these results enables research and software development groups to identify the features that can increase the accuracy of a CDSS as well as the features that distract decision making across the medical spectrum.

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Figure 1.
The Children's Hospital Resource In Selecting Therapy Individualized Expert framework.

Figure 2.
The test of stability of clusterings.

Table 1

Survey participant characteristics

Characteristics	<i>N</i>
Female	7
Male	16
Pediatric	22
Non-pediatric	1
Average years since medical school graduation (SD)	24.5 (8.6)

Table 2

Drug feature validations with number of factors used in recommendation scoring

Initial features [number of factors]	Revised features
Drug-related CNS side effects (behavioral/psychiatric/cognitive effects) [12]	AED: Potential for CNS side effects (behavioral/psychiatric/cognitive effects)
Drug-related whole-body side effects (weight effects) [12]	AED: Potential for whole-body side effects (weight effects)
Drug-related non-CNS side effects (hematologic, hepatic, etc.)	AED: Potential for non-CNS side effects (hematologic, hepatic, etc.)
Drug-related chronic toxicities [18]	AED: Potential for chronic toxicities
Drug-related idiosyncratic reaction [12]	AED: Potential for idiosyncratic reaction
Drug-related teratogenic effect (age related) [3]	AED: Potential for teratogenic effect (age related)
Drug-related mutagenic effect [6]	
Drug practical issues (formulation available for this age, dosing interval) [30]	AED: Practical issues (formulation available for this age, dosing interval)
	AED: Cost
Drug pharmacokinetic characteristics (protein binding, half-life) [30]	AED: Pharmacokinetic characteristics (protein binding, half-life)

Table 3

Patient feature validations with number of factors used in recommendation scoring

Initial features [number of factors]	Revised features
Drug efficacy [44]	Patient: Seizure type Patient: Epilepsy syndrome
Drug effect on patient co-morbidities (e.g., patient overweight/migraines) [120]	Patient: Co-morbid weight disorder (obesity, underweight) Patient: Co-morbid psychiatric disease (depression, anxiety, etc.) Patient: Co-morbid neurological disease (migraine, mental retardation) Patient: Co-morbid other systemic disorders (asthma, arthritis, diabetes, etc.)
Drug-drug interactions [191]	Patient: Concomitant medications (potential for drug-drug interactions) Patient: Concomitant environmental factors (potential for drug-environment interactions)
Patient demographics (gender, race, ethnicity) [42]	Patient: Gender Patient: Race and ethnicity
Patient pubertal status [18]	
Patient history of drug rashes [12]	Patient: History of drug rashes
Patient history of poor adherence to medication usage [12]	Patient: History of poor adherence to medication usage
Patient co-morbidity effect on drug (e.g., decreased hepatic/renal function) [30]	Patient: Co-morbid decreased hepatic/renal function
Family history of response to this drug or class of drugs [2]	Patient: Family history of response to this drug or class of drugs
Genetic laboratory tests for drug efficacy [6]	Patient: Genetic laboratory tests for AED efficacy
Genetic laboratory tests for drug metabolism [6]	Patient: Genetic laboratory tests for AED metabolism
Non-genetic disease-related laboratory findings (EEG, MRI) [42]	Patient: EEG findings Patient: MRI findings
Non-genetic non-disease-related laboratory findings (CBC, liver panel) [16]	Patient: Hematologic function at time of drug selection (measured by CBC) Patient: Liver panel/function at time of drug selection (measured by LFTs)
Previous drug response [2]	Patient: Previous response to AEDs

Table 4

Feature ranking and survey mean scores (SD) by age group

Question	Cluster	All	1–23 months	2–12 years	>12 years
Seizure type	5 (100%)	4.95 (0.11)	4.91 (0.28)	4.96 (0.2)	5 (0)
Epilepsy syndrome	5 (100%)	4.91 (0.29)	4.91 (0.28)	4.96 (0.2)	4.88 (0.45)
EEG	5 (100%)	4.55 (0.71)	4.52 (0.77)	4.61 (0.77)	4.58 (0.72)
Previous AED response	4 (96%)	4.2 (0.76)	3.96 (1.12)	4.09 (0.97)	4.12 (1.15)
CNS side effects	4 (96%)	4.16 (0.64)	3.91 (1.02)	4.22 (0.72)	4.46 (0.78)
Whole-body side effects	4 (100%)	3.84 (0.51)	3.17 (1.2)	3.91 (0.72)	4.42 (0.5)
Concomitant medications	4 (100%)	3.84 (0.67)	4.04 (0.91)	3.83 (1.01)	3.79 (0.88)
Practical issues	4 (96%)	3.74 (0.91)	3.96 (1)	3.87 (0.8)	3.38 (1.28)
Comorbid weight disorder	4 (100%)	3.68 (0.55)	2.87 (1.12)	4 (0.59)	4.12 (0.74)
History of drug rash	3 (87%)	3.67 (1.03)	3.61 (1.34)	3.52 (1.14)	3.62 (1.06)
MRI	3 (87%)	3.48 (1.09)	3.39 (1.13)	3.48 (1.28)	3.54 (1.18)
Chronic toxicities	4 (100%)	3.46 (0.87)	3.52 (1.06)	3.3 (1.04)	3.54 (1.02)
Comorbid neurological disease	3 (91%)	3.28 (0.68)	2.7 (1.12)	3.61 (0.82)	3.58 (0.88)
Non-CNS side effects	3 (96%)	3.27 (0.83)	3.43 (1.01)	3.13 (0.95)	3.17 (1.05)
History of poor adherence	3 (91%)	3.22 (1)	2.83 (1.4)	3.09 (1.18)	3.42 (1.06)
Com psych disease	3 (91%)	3.21 (0.72)	1.78 (1.41)	3.7 (0.8)	4 (0.78)
Pharmacokinetics	3 (91%)	3.18 (0.93)	3.3 (1.16)	3.04 (1.04)	3.17 (0.87)
Co-morbid hepatic/renal disease	2 (96%)	3.03 (1.17)	3 (1.14)	2.91 (1.35)	2.96 (1.43)
Liver functions	2 (96%)	2.74 (1.18)	2.57 (1.35)	2.7 (1.23)	2.75 (1.39)
Idiosyncratic reaction	3 (83%)	2.68 (1.12)	2.65 (1.2)	2.57 (1.25)	2.62 (1.17)
Hematologic functions	2 (96%)	2.68 (1.27)	2.59 (1.37)	2.57 (1.38)	2.67 (1.4)
Cost	3 (78%)	2.64 (0.99)	2.26 (1.29)	2.55 (1.09)	2.79 (1.14)
Teratogenic effect	2 (100%)	2.6 (1.04)	1.17 (1.63)	2.09 (1.41)	4.33 (0.92)
Family history AED class response	3 (87%)	2.59 (1.36)	2.39 (1.41)	2.57 (1.5)	2.5 (1.56)
Co-morbid other systems disorders	2 (100%)	2.48 (1.05)	2.43 (1.35)	2.43 (1.06)	2.29 (1.3)
Gender	2 (100%)	2.36 (1.01)	0.39 (0.92)	2.57 (1.53)	3.96 (1.4)
Concomitant environmental interactions	2 (100%)	2.15 (1.27)	2.26 (1.51)	2 (1.38)	2 (1.47)
Genetics/efficacy	1 (100%)	1.19 (1.1)	1.64 (1.49)	0.83 (1.2)	0.96 (1.23)

Question	Cluster	All	1-23 months	2-12 years	>12 years
Race ethnicity	1 (100%)	1.15 (1.32)	0.83 (1.31)	1.13 (1.39)	1.35 (1.46)
Genetics/metabolism	1 (100%)	0.91 (1.14)	1 (1.35)	0.87 (1.19)	0.75 (1.03)

Table 5

Anti-epileptic drugs selection clusters

Cluster	Weight (SD)
Disease characteristics – <i>EEG, seizure type & syndrome</i>	4.8 (0.049)
Drug toxicities – <i>Previous AED response, CNS side effects, whole-body side effects, concomitant drug–drug interaction, practical issues, co-morbid weight disorders, chronic toxicities</i>	3.82 (0.098)
Medical history – <i>History of drug rash, MRI, co-morbid neurological disease, non-CNS side effects, history of poor adherence, co-morbid psychiatric disease, pharmacokinetics, idiosyncratic reaction, cost, family history of AED response</i>	3.12 (0.102)
Systemic characteristics – <i>Co-morbid renal disease, liver functions, hematological functions, teratogenic effect, other co-morbid systematic disorders, gender, concomitant environmental drug–drug interaction</i>	2.57 (0.048)
Genetic characteristics – <i>Genetic efficacy, race, genetic metabolism</i>	1.08 (0.046)