FULL-LENGTH ORIGINAL RESEARCH

The current state of epilepsy guidelines: A systematic review

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Summary

Objective: **The International League Against Epilepsy (ILAE) Epilepsy Guidelines Task Force, composed of 14 international members, was established in 2011 to identify, using systematic review methodology, international epilepsy clinical care guidelines, assess their quality, and determine gaps in areas of need of development.**

Methods: **A systematic review of the literature (1985–2014) was performed in six electronic databases (e.g. Medline, Embase) using a broad search strategy without initial limits to language or study design. Six gray literature databases (e.g., American Academy of Neurology [AAN], ILAE) were also searched to minimize publication bias. Two independent reviewers screened abstracts, reviewed full text articles, and performed data abstraction. Descriptive statistics and a meta-analysis were generated.**

Results: **The search identified 10,926 abstracts. Of the 410 articles selected for full text review, 63 met our eligibility criteria for a guideline. Of those included, 54 were in English and 9 were in other languages (French, Spanish, and Italian). Of all guidelines, 29% did not specify the target age groups, 27% were focused on adults, 22% included only children, and 6% specifically addressed issues related to women with epilepsy. Guidelines included in the review were most often aimed at guiding clinical practice for status epilepticus (n = 7), first seizure (n = 6), drug-resistant epilepsy (n = 5), and febrile seizures (n = 4), among others. Most of the guidelines were therapeutic (n = 35) or diagnostic (n = 16) in nature. The quality of the guidelines using a 1–7 point scale (7 = highest) varied and was moderate overall (mean = 4.99 ± 1.05 [SD]).**

Significance: **We identified substantial gaps in topics (e.g., epilepsy in the elderly) and there was considerable heterogeneity in methodologic quality. The findings should offer a valuable resource for health professionals caring for people with epilepsy, since**

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they will help guide the prioritization, development, and dissemination of future epilepsy-related guidelines.

KEY WORDS: Epilepsy guidelines, Evidence-based medicine, Clinical practice guidelines.

Key Points

- Sixty-three clinical practice guidelines were identified on 19 populations/conditions covering most age groups
- The focus of the guidelines was most commonly therapeutic, followed by diagnostic and overall epilepsy management
- Twenty-eight countries were represented in the guideline development committees, and the included guidelines were written in four languages
- The total quality of the guidelines was rated as moderate with significant heterogeneity in quality between guidelines
- This study provides a foundation to guide future development of epilepsy guidelines in high priority areas of epilepsy care

Evidence and knowledge concerning the clinical care of persons with epilepsy is growing exponentially. As a result, it is challenging for treating health professionals to remain current with the literature that guides evidence-based care for persons with epilepsy. Clinical practice guidelines (CPGs) are systematically created to assist health professionals optimize care in specific circumstances, based on the best available evidence and expert clinical judgment.[1,2] The recommendations within a CPG are not only based on a comprehensive evaluation of the available evidence but also take into consideration the risks and benefits of the intervention or treatment at hand, using the clinical judgment of an expert panel.[1–8] A CPG should also include a detailed description of the development process and methods, the results of the literature search, and suggestions for implementing recommendations into practice.[1–3,5,8,9]

Because CPGs are evidence based and provide recommendations for care, they are often used to develop policy and quality indicators,[10] and they can also influence reimbursement of health services.[11] Regular use of CPGs can improve processes of care and patient outcomes across various disciplines.[12] For example, a cardiac care study found that when CPG recommendations were followed, patients had lower rates of heart failure, recurrence of atrial fibrillation, and hospitalizations.[13] Unfortunately, this has not necessarily been the experience in epilepsy,[14,15] most likely because of the poor adoption of CPG recommendations into routine clinical practice.[14–17]

Although CPGs can be useful for health professionals and have widespread application beyond the clinical setting, they are not without limitations. As with the general medical literature, the number of CPGs is rising exponentially, making it difficult to determine which CPG should be consulted. At the same time there are no universally accepted standards for developing or reporting standards for CPGs. Lack of standards can result in heterogeneity in the quality of CPGs and inconsistencies among recommendations for the same clinical scenario. CPGs addressing epilepsy care are not exempt from these limitations, and there is a need to examine available CPGs for persons with epilepsy.

The present study was undertaken to review existing CPGs for the care of persons with epilepsy using systematic methodology to assess their quality. The study is also aimed at identifying gaps in the availability and quality of these CPGs and to provide an improved knowledge basis to guide development of future CPGs in this area.

Methods

Search strategy

The search strategy, developed in consultation with a librarian with expertise in health research and systematic reviews, included terms related to epilepsy or seizures, and guidelines (Appendix S1). A broad approach was taken through the inclusion of all possible synonyms and abbreviations for the terms of interest, and controlled vocabulary/subject headings (including MeSH, EmTree). The search strategy was run on December 8, 2014, in six of the largest medical databases: Medline, Embase, Cochrane Central, Cochrane systematic review, PsycINFO, and CINAHL. To minimize publication bias, the same terms were used to search gray literature sources including National Guideline Clearinghouse, Guideline International Network, the American Academy of Neurology, the American Epilepsy Society, the International League Against Epilepsy, the Scottish Intercollegiate Guideline Network, and the National Institute for Health and Care Excellence. The search strategy was limited to humans, and to studies published after 1985.

Study selection and eligibility criteria

The title and abstracts of the identified references were screened in duplicate by two independent reviewers (NJ and

KS) to identify references for full-text screening to determine inclusion. The two independent reviewers screened the first 100 references together to ensure consistent abstraction. If there was disagreement between the reviewers at the title and abstract screening phase, the reference was included for full-text screening.

The full text of included references was also screened by at least two independent reviewers to determine if they met the inclusion criteria (KS acted as first reviewer and all authors acted as second reviewers). A standardized database was used for full-text review, which included reason for exclusion and basic study characteristics. The full-text review process (including the standardized data abstraction form) was pilot tested using three of the included CPGs with all reviewers to ensure consistency. If there was disagreement between reviewers, a third reviewer (NJ) was consulted.

Studies were included if they met the adopted definition of a CPG,[1,2] namely, if they included recommendations for the care of persons with epilepsy, they were developed by a group, they were evidence-based, and the quality or level of the evidence and/or recommendation was stated. Studies were not excluded based on language initially.

Data abstraction and CPG quality

Data abstraction was completed in duplicate by two independent reviewers (KS acted as first reviewer and all authors acted as a second reviewer), using a standardized data abstraction form. If there were discrepancies in data abstraction between reviewers, the reviewers discussed the discrepancy and, when necessary, a third reviewer (NJ) was consulted when needed.

Study characteristics included: year of publication, number of CPG development group members, ILAE region in which the CPG was developed, professional organizations that endorsed the CPG, the level of evidence used to formulate the recommendations, and the number of clinical care recommendations. The characteristics of the target population for the CPG were also abstracted and included age, sex, target population or condition, as well as the focus of the CPG (e.g., diagnostic, therapeutic, or management). The recommendations for clinical care were also abstracted.

The quality of the CPGs was evaluated using the AGREE II tool,[18] which assesses quality using six domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, editorial independence, and applicability using a 7-point Likert scale (whereby 7 is the highest quality).[18] An "overall" quality rating was also assigned using a 7-point Likert scale, which is independent of the ratings for each domain. The AGREE II tool was developed in response to the lack of standards or method for evaluating the quality of CPGs, based on a literature review and field testing by international CPG experts.[19] The AGREE II has been tested for reliability and validity and has undergone revisions based on feedback.[18] The AGREE II tool does not provide cutoff scores that allow the user to determine if a CPG is of "high" or "low" quality. For the purposes of this study, we have defined a quality rating of 5 or greater (71%) as a high quality CPG, whereas anything below that was deemed to be of lower (inadequate) quality. Using these criteria, the proportion of high-quality CPGs was determined.

Data synthesis and analysis

Descriptive statistics and frequencies were generated for the study characteristics, clinical characteristics of the target population, and CPG quality.

Due to the nature of the data abstracted, a meta-analysis was possible only for CPG quality. A random effects model using the metaprop package for STATA 12.0,[20,21] was employed to examine the heterogeneity of the CPG quality using the total AGREE II score (out of 161).

Linear regression was used to test the a priori hypothesis that CPG characteristics (number of committee members, number of recommendations, and year of publication) predict the quality of the CPGs, as measured by the AGREE II tool. Multivariate linear regression was also used to identify domains of the AGREE II tool that were related to the overall AGREE II rating. Partial correlations and their corresponding R^2 using the pcorr2 package in STATA, were examined to determine the amount of variance explained by each of the six AGREE II domains, while the remaining domains were included in the model.

All data analyses were conducted using STATA 12.0.[22] Relationships were considered statistically significant for p-values <0.05.

This study was approved by the Conjoint Health Research Ethics Board at the University of Calgary.

Results

Study selection

The search strategy produced 10,926 references after duplicates were removed, of which 410 articles were selected for full-text review (Fig. 1). Of these, 63 CPGs met all eligibility criteria for data abstraction. The remaining 347 were excluded because they were: (1) not a CPG (e.g., literature reviews, expert opinions, and consensus statements); (2) a CPG without evaluation of the evidence; (3) a technical CPG not pertaining to clinical care; (4) a duplicate CPG (e.g., one CPG published in multiple journals); (5) a CPG not specific to epilepsy or EEG; (6) a CPG in a language for which we were unable to find a reviewer fluent in that language (Finnish, n = 4); or (7) a CPG for which we were unable to locate a copy (Fig. 1). For CPGs with published updates, we selected the most recent CPG, and the excluded version(s) were deemed to be duplicates.

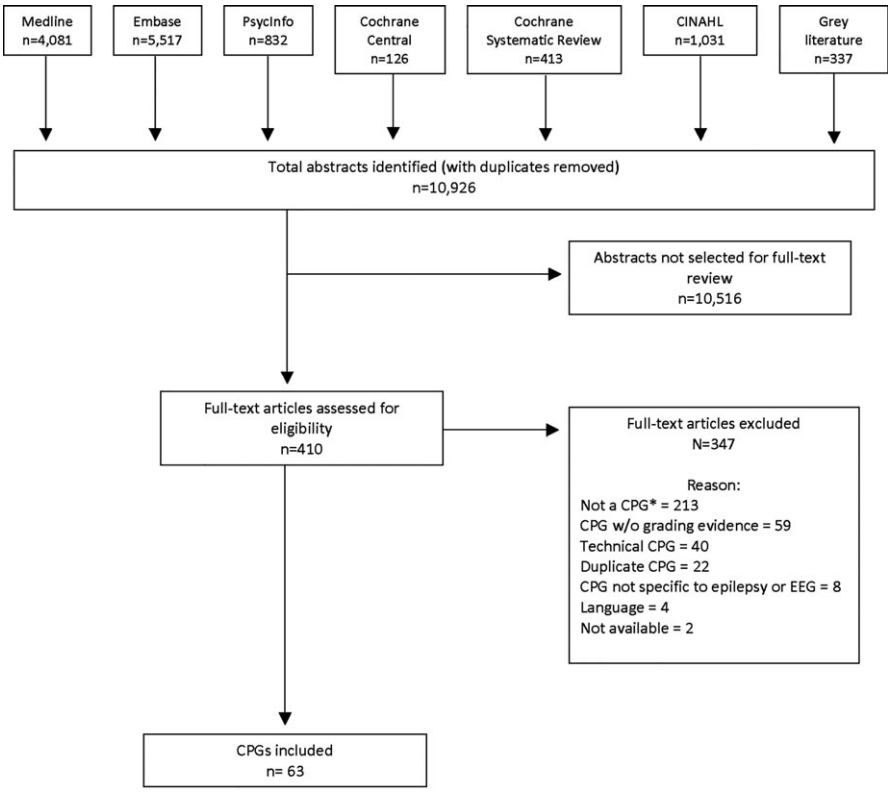

Figure 1.
Flow diagram of flow of information through the systematic review.
Epilepsia © ILAE

CPG characteristics

Sixty-three CPGs met the inclusion criteria and were included in this systematic review (Appendix S2). Characteristics of each CPG are listed in Table 1—the CPGs that are of high quality (≥5 of 7) are indicated by[a].

The ILAE regions represented in the development committees of included CPGs were most commonly North America (n = 33; 52.4%) and Europe (n = 33; 52.40%). Other ILAE regions represented included Latin America (n = 4; 6.3%), Asia and Oceania (n = 3; 4.8%), and Africa (n = 1; 1.6%). The number of CPGs by region exceeds the number of included CPGs, because the CPG development committee often had representation from more than one ILAE region. The number of CPG development committee members ranged from 3 to 40 (mean = 12.8; SD = 8.3).

The number of recommendations varied between CPGs with a mean number of 17.0 (SD = 37.4) and a median of 8 (range 1–285) recommendations. The mean and median year of publication was 2007 (SD = 4.47 years).

Characteristics of the target populations/conditions

The target population or condition was most commonly classified, broadly, as all epilepsies (n = 16; 25.4%), included both genders (n = 59; 93.7%), and focused on therapeutic aspects of clinical care (n = 35; 55.6%) (Table 2). Age of the target population of the included CPGs was most commonly not specified (n = 18; 28.6%); followed by adults (n = 17; 27.0%), children (n = 14; 22.2%), all ages (n = 13; 20.6%), and infants (n = 1; 1.6%). There were no CPGs focusing on epilepsy in the elderly.

Study quality

The mean overall CPG quality was rated 4.99 on the 7-point scale (71.29%; SD = 1.05). Using a cutoff of 5 (71%) of 7, 46 (73%) of the CPGs were considered high quality, whereas 17 (27%) were of poorer quality. The mean proportions for each of the six AGREE II domains (out of 7) are presented in Figure 2. The domains rated most highly were scope and purpose followed by clarity, rigor of development, editorial independence, and stakeholder involvement; applicability was rated the lowest.

Meta-analysis of the total score of the AGREE II tool, revealed a pooled estimate of quality of 63% (0.63) of the total possible score (95% CI 0.60–0.66). A significant amount of heterogeneity between the quality of CPGs was found (I^2 = 90.70%, $p < 0.0001$) (Fig. S1).

The domains that were positively associated with the overall quality score of the AGREE II tool were rigor of development ($t = 5.97$, $p < 0.001$) and clarity of presentation ($t = 4.56$, $p < 0.001$). There was, however, a trend toward an inverse relationship between scope and purpose and a high overall quality score of the AGREE II tool in multivariate analysis ($t = -1.87$, $p = 0.07$). The multivariate

Table 1. Guideline characteristics

Author (year)	ILAE region(s) represented (countries)	Endorsed by	Number of committee members	Number of recommendations	Age	Sex	Population/ condition	Focus	Quality (/7)[a]
[a]Armon (2003)	Europe (UK)	None	30	16	Child	Both	Febrile seizure	Diagnostic (n = 7) Prognostic (n = 3) Admission criteria (n = 4) Management (n = 2)	5.5
[a]Baird (2013)	North America (Canada, U.S.A.)	AAN	5	2	All ages	Both		Neurocysticercosis	
Therapeutic	5.5								
Bascic-Kes (2012)	Europe (Croatia)	CSND, CMA	7	1	Adults	Both	Drug resistant epilepsy	Therapeutic	3
[a]Baumer (2004)	Europe (UK)	None	NS	20	Child, infant	Both	Presenting to ED with seizure	Diagnostic (n = 15) Prognostic (n = 1) Admission criteria (n = 3) Management (n = 1)	5
[a]Beghi (2006)	Europe (Italy)	LICE	4	13	NS	Both	First seizure	Therapeutic (n = 4) Diagnostic (n = 9)	5
[a]Beghi (2008)	Europe (Italy)	LICE	4	13	All ages	Both	First seizure	Diagnostic	5
[a]Beghi (2013)	Europe (Italy)	LICE	11	16	All ages	Both	Withdrawal of AEDs	Therapeutic	5
Bernater (2006)	Latin America (Argentina)	None	31	7	NS	Both	New onset epilepsy	Therapeutic	2
[a]Birbeck (2012)	Europe (Italy), North America (U.S.A.), Africa (Zambia)	ILAE, AAN	10	8	NS	Both	Epilepsy associated with AIDS/HIV	Therapeutic	6
Boon (2012)	Europe (Belgium)	None	10	6	All ages	Both	All epilepsies	Therapeutic	4
[a]Brathen (2005)	Europe (UK, Ireland, Spain, Italy, Hungary Finland, Sweden)	EFNS	9	11	NS	Both	Alcohol-related seizures	Therapeutic (n = 5) Diagnostic (n = 5) Prognostic (n = 1)	6
[a]Bratton (2007)	Europe (Netherlands), North America (U.S.A.), Latin America (Argentina)	None	17	2	NS	Both	Post-traumatic seizures	Therapeutic	5
[a]Brophy (2012)	North America (U.S.A.)	NCS	12	21	All ages	Both	Status epilepticus	Therapeutic (n = 1) Diagnostic (n = 3) Definition (n = 16) Management (n = 1)	5
Burgunder (2010)	Europe (Austria, Belgium, Ireland, Italy, Germany, Norway, France, Switzerland, Hungary)	EFNS	17	2	All ages	Both	All epilepsies	Diagnostic	4

Continued

Table 1. Continued.

Author (year)	ILAE region(s) represented (countries)	Endorsed by	Number of committee members	Number of recommendations	Age	Sex	Population/ condition	Focus	Quality (/7)[a]
Caplin (2006)	North America (U.S.A.)	None	13	30	0-18 years	Both	Uncomplicated epilepsies	Management	4
Capovilla (2009)	Europe (Italy)	LICE	4	19	Child	Both	Febrile seizure	Therapeutic (n = 2) Diagnostic (n = 12) Admission criteria (n = 5)	4.5
[a]Capovilla (2013)	Europe (Italy)	LICE	6	16	Child	Both	Status epilepticus	Therapeutic (n = 14) Diagnostic (n = 1) Management (n = 1)	5
Chandra (2010)	Asia & Oceania (India)	None	3	3	NS	Both	Drug resistant epilepsy	Therapeutic (n = 1) Diagnostic (n = 1) Definition (n = 1)	2.5
[a]Chang (2003)	North America (U.S.A.)	AAN	14	2	Adult	Both	Traumatic brain injury	Therapeutic	6
[a]Claassen (2013)	Europe (Italy, Belgium, Germany, Switzerland), North America (U.S.A.)	ESICM	6	4	NS	Both	Status epilepticus	Diagnostic	5.5
[a]Consalvo (2013)	Latin America (Argentina)	SNA	6	11	NS	Both	All epilepsies	Therapeutic	5
Crawford (1999)	Europe (England, Ireland, Scotland, Wales)	None	8	45	Adult	Female	Women with epilepsy	Therapeutic (n = 11) Diagnostic (n = 2) Prognostic (n = 11) Management (n = 21)	4
[a]Dougherty (2008)	North America (U.S.A.)	AAP	18	1	6–60 month	Both	Febrile seizures	Therapeutic	6
[a]Duffner (2011)	North America (U.S.A.)	AAP	7	6	6-60 month	Both	Febrile seizures	Diagnostic	6
Elovaara (2008)	Europe (Finland, Norway, Denmark, Netherlands, England, Serbia)	None	10	1	NS	Both	Rasmussen's encephalopathy	Therapeutic	4
[a]Engel (2003)	NS	ILAE, AAN	10	2	NS	Both	Drug-resistant epilepsy	Therapeutic	6
[a]Fountain (2011)	North America (U.S.A.)	AAN	40	8	NS	Both	All epilepsies	Quality of Care Indicators	5
[a]French (2007)	North America (U.S.A.)	AAN	4	11	All ages	Both	All epilepsies	Therapeutic	5
[a]French (2007)	North America (U.S.A.)	AAN	4	9	All ages	Both	All epilepsies	Therapeutic	5
[a]French (2007)	North America (U.S.A.)	AES, AAN	24	2	All ages	Both	New-onset epilepsy	Therapeutic	5
[a]Gilbert (2000)	North America (U.S.A.)	AAN	12	7	Child	Both	First seizure	Diagnostic	5.5
[a]Glantz (2000)	North America (U.S.A.)	None	12	2	NS	Both	Brain tumor	Therapeutic	5.5
[a]Glauser (2006)	Europe (Sweden, England, Finland, Italy), Latin America (Brazil), North America (U.S.A.)	ILAE	10	26	Child, Adult, Older adult	Both	All epilepsies	Therapeutic	5.5

Continued

Table 1. Continued.

Author (year)	ILAE region(s) represented (countries)	Endorsed by	Number of committee members	Number of recommendations	Age	Sex	Population/ condition	Focus	Quality (/7)[a]
[a]Go (2012)	Asia & Oceania (Australia), (U.S.A., Canada)	AES, AAN, CNS	7	8	Infants	Both	Infant spasms	Therapeutic	5
[a]Harden (2009)	North America (U.S.A.)	AES, AAN	20	7	Reproductive age	Female	Women with epilepsy	Prognostic	6
[a]Harden (2009)	North America (U.S.A.)	AAN	20	8	Reproductive age	Female	Women with epilepsy	Therapeutic (n = 2) Prognostic (n = 3) Management (n = 3)	6
[a]Harden (2009)	North America (U.S.A.)	AAN	22	20	Reproductive age	Female	Women with epilepsy	Therapeutic (n = 16) Management (n = 4)	6
[a]Hirtz (2003)	North America (U.S.A.)	AAN, CNS	35	2	0–18 years	Both	First seizure	Therapeutic	5.5
[a]Huff (2014)	North America (U.S.A.)	ACEP, ENA	6	8	Adults	Both	First seizure	Therapeutic (n = 7) Admission criteria (n = 1)	5.5
Kerr (2001)	Europe (U.K., Italy, Sweden, Finland), Asia & Oceania (New Zealand, Australia), North America (U.S.A.)	IASSID	22	16	NS	Both	Persons with developmental disabilities	Diagnostic (n = 14) Services provision risk assessment & adjustment	4.5
[a]Krumholz (2007)	North America (U.S.A.)	AAN	17	6	Adult	Both	First seizure	Diagnostic	6.5
Ma (2010)	NS	PCC	4	19	Child	Both	Status epilepticus	Therapeutic (n = 9) Diagnostic (n = 3) Prognostic (n = 2) Management (n = 3) Monitoring Definition	3.5
[a]Meierkord (2010)	Europe, Western (Germany, U.K., Italy, Norway, Belgium)	EFNS	7	19	Adults	Both	Status epilepticus	Therapeutic (n = 14) Management (n = 4) Local guidance	5
[a]Mercade-Cerda (2009)	Europe (Spain)	SEN, SAE	5	10	NS	Both	Traumatic brain injury	Therapeutic	6
[a]Mikkelse (2010)	North America (U.S.A., Canada)	AANS	14	1	Adults	Both	Brain tumor	Therapeutic	5
[a]Minicucci (2006)	Europe (Italy)	LICE	6	15	Adults	Both	Status epilepticus	Therapeutic	5
[a]Morris (2013)	North America (U.S.A., Canada)	AAN	6	6	All ages	Both	All epilepsies	Therapeutic	5
[a]NICE (2012)	Europe (England)	NICE	13	285	All ages	Both	All epilepsies	Management	6
[a]No author (2004)	North America (U.S.A.)	ACEP	NS	10	Adult	Both	New-onset epilepsy and status epilepticus	Therapeutic (n = 2) Diagnostic (n = 6) Admission criteria (n = 2)	5
[a]No author (1996)	North America (U.S.A.)	AAN	14	1	All ages	Both	AED reduction	Therapeutic	5.5
No author (2004)	Europe (France)	None	NS	4	Adult	Both	Drug-resistant epilepsy	Therapeutic	4

Continued

Table 1. Continued.

Author (year)	ILAE region(s) represented (countries)	Endorsed by	Number of committee members	Number of recommendations	Age	Sex	Population/ condition	Focus	Quality (/7)[a]
[a]Pietrzak (1996)	North American (U.S.A.)	AAN, AANS	9	7	NS	Both	Presenting to ED with seizures	Diagnostic	6
[a]Pruna (2013)	Europe (Italy)	LICE	11	6	Child	Both	All epilepsies	Vaccination	5.5
[a]Riviello (2006)	North America (U.S.A.)	AES, AAN, ACEP, AAP	10	12	1 month-19 years	Both	Status epilepticus	Diagnostic	5.5
[a]Sanchez-Alvarez (2005)	Europe (Spain)	SEN, SAE	11	16	NS	Both	Drug-resistant epilepsy	Therapeutic	5
Sanchez-Alvarez (2005)	Europe (Spain)	SEN, SAE	11	39	All ages	Both	All epilepsies	Therapeutic	2
Serrano-Castro (2005)	Europe (Spain)	SEN, SAE	11	29	Adults	Both	All epilepsies	Therapeutic	3
Serrano-Castro (2005)	Europe (Spain)	SEN, SAE	11	6	NS	Both	All epilepsies	Therapeutic	3
[a]Shah (2014)	North America (U.S.A., Canada)	PEMAC	9	15	Child	Both	All epilepsies	Therapeutic (n = 9) Diagnostic (n = 6)	6
[a]Smirniotopoulos (2011)	North America (U.S.A.)	None	14	1	NS	Both	Drug-resistant epilepsy	Diagnostic	5
Yablon (1998)	North America (U.S.A.)	AAPMR	3	3	Adults	Both	Traumatic brain injury	Therapeutic	3
[a]SIGN (2003)	Europe (Scotland)	SIGN	25	97	Adults	Both	All epilepsies	Management	6
[a]SIGN (2003)	Europe (Scotland)	SIGN	25	44	Child	Both	All epilepsies	Management	6

NS, Not Specified; AAN, American Academy of Neurology; AANS, American Academy of Neurological Surgeons; AAPMR, American Academy of Physical Medicine and Rehabilitation; AAP, American Academy of Pediatrics; ACEP, American College of Emergency Physicians; AES, American Epilepsy Society; CMA, Croatian Medical Association; CNS, Child Neurological Society; CSND, Croatian Society for Neurovascular Disorders; ED, Emergency Department; EFNS, European Federation of Neurological Societies; ENA, Emergency Nurses Association; ESICM, European Society of Intensive Care Medicine; IASSID, International Association for the Scientific Study of Intellectual Disabilities; ILAE, International League Against Epilepsy; LICE, Lega Italiana Contro L'Epilessia; NCS, Neurocritical Care Society; NICE, National Institute for Health and Care Excellence; PCC, Pediatric Coordinating Committee; PEMAC, Pediatric Emergency Medicine Advisory Committee of the Maryland Institute for EMS systems; SAE, Sociedad Andaluza de Epilepsia; SEN, Sociedad Española de Neurología; SIGN, Scottish Intercollegiate Guidelines Network; SNA, Sociedad Neurológica Argentina.

[a]CPGs of high quality.

Table 2. Target population/condition and focus of CPGs

Population/condition	Frequency	Percent (%)
Alcohol-related seizures	1	1.6
All epilepsies	16	25.4
Status epilepticus	7	11.1
First seizure	6	9.5
Drug-resistant epilepsy	5	8.0
Women with epilepsy	4	6.4
Febrile seizure	4	6.4
Traumatic brain injury	3	4.8
New-onset epilepsy	3	4.8
Discontinuation of AEDs	2	3.2
Brain metastases	2	3.2
Epilepsy associated with HIV/AIDS	1	1.6
Infantile spasm	1	1.6
Neurocysticercosis	1	1.6
Presenting to the ED with seizures		
Child	1	1.6
Adult	1	1.6
Status epilepticus	1	1.6
Monotherapy for partial seizures	1	1.6
Uncomplicated epilepsy	1	1.6
Development disability	1	1.6
Posttraumatic seizures	1	1.6
Focus		
Therapeutic	35	55.6
Diagnostic	16	25.4
Management	10	15.9
Quality indicators	1	1.6
Vaccination	1	1.6

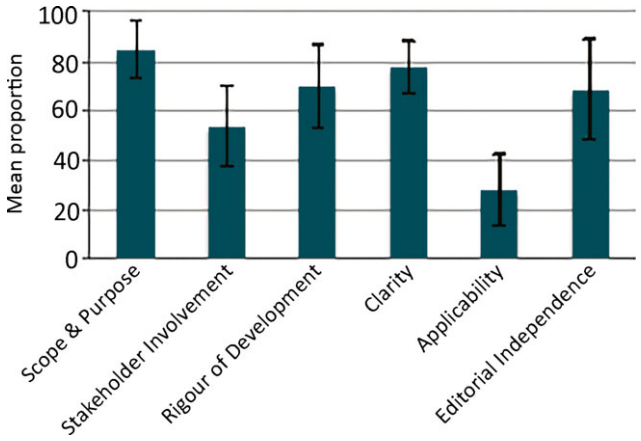

Figure 2.
The mean percent quality of included CPGs for each of the six AGREE II quality domains.
Epilepsia © ILAE

model, with all six domains included, explained 77.36% of the variance in the overall quality score of the AGREE II tool. Examination of partial correlations revealed that only two domains resulted in a significant change in the variance when they were added to the model. The rigor of development domain accounted for 38.92% of the variance, when the remaining domains were held constant ($p < 0.001$); whereas clarity accounted for 27.10% variance, when the remaining domains were held constant ($p < 0.001$). Univariate regression showed that none of the study characteristics (number of committee members, number of recommendations, and year of publication) were associated with the quality of the CPGs, as measured by the AGREE II tool using the overall score and the total AGREE II score.

Discussion

This study identified 63 CPGs for the care of persons with epilepsy that covered most age groups and many populations/conditions. There was considerable heterogeneity between included CPGs, especially with regard to CPG development methodology and reporting and quality of CPGs.

Inconsistent, nonstandard terminology to distinguish CPGs from other types of publications is a major concern, because it may seriously mislead readers. Some authors call expert opinions, literature reviews (systematic or not), or the opinion of a group of experts (derived through a consensus method or not) "guidelines," but these products cannot be labeled as CPGs based on standard definition criteria.[1,2] This issue is highlighted in our study, where of the 410 articles reviewed in full text, 213 (52%) were excluded because on closer examination they were a literature review, consensus statement, or expert opinion, and so on. An additional 59 (14%) CPGs were excluded because while they were CPGs (synthesis of the evidence and recommendations for care, by a group) they failed to meet the criteria of evaluating or grading the evidence on which the recommendations were based. The inconsistent use of terminology for CPGs may be related to the lack of standardized methodology for developing and reporting of CPGs, which may in turn account for some of the heterogeneity in CPG quality found in this study.

The quality of the CPGs was only moderate (71.29%) and 27% were of poor quality despite the fact that we only included CPGs that were developed using rigorous methodology (e.g. evidence graded). The inclusion of more rigorous CPGs likely inflated the overall quality of articles published in this area—indeed rigor of development was one of the strongest predictors of CPG quality.

A potential source of heterogeneity among CPGs may be the variance in scores between the domains of the AGREE II tool. For example, although the scope and purpose was often rated highly, CPG applicability was rated low. The consistently low applicability ratings on the AGREE II tool are particularly concerning. Although CPGs have been found in a variety of clinical settings, to improve the quality of care in a variety of clinical settings,[23] improvements can occur only if CPGs are implemented in clinical practice. Practical implementation of CPGs remains a challenge, especially in epilepsy,[14,15,17] and lack of applicability of CPGs has been cited as a reason for limited adoption of CPGs in clinical practice.[24] Other cited reasons for not

adopting CPGs in everyday practice include lack of awareness, lack of familiarity, lack of agreement, lack of outcome expectancy, lack of self-efficacy, lack of motivation, guideline factors (CPG characteristics, contradictory recommendations), and environmental factors.[24] Studies examining barriers and facilitators to the application of CPGs in managing persons with epilepsy are needed to develop effective targeted implementation strategies. Furthermore, the methods for creating CPGs need to be clearly delineated, and these methods should place the target user at the center of the CPG development, which should improve the applicability of the proposed CPG.[25] As such, to maintain credibility and accessibility of the CPGs it is imperative that a professional organization such as the International League Against Epilepsy (ILAE), play a key role in epilepsy CPG development. A recently published CPG development toolkit and handbook by the ILAE Epilepsy Guidelines Working Group is a major step toward improving future epilepsy CPGs.[26]

The CPGs identified in this systematic review were on average (mean) 7 years old. A recent analysis of the recommendations found in the Spanish National Health System CPGs developed since 2008 revealed that >20% of recommendations made in these CPGs became outdated within 3 years, and that number increases to 22.2% within 4 years.[27] Based on these findings, it is recommended that CPGs be updated at least every 3 years.[27] By these criteria, 71.43% of existing CPGs for persons with epilepsy can be considered at risk of being outdated. This also depends, however, on the specific field and topic addressed by a guideline.

The CPGs included in the present study covered 19 populations and/or conditions, and most age groups. Despite this diversity, there were clear gaps in availability of CPGs for important clinical scenarios related to the care of persons with epilepsy. In considering the heterogeneity of epilepsy,[28] there are many populations and epilepsy syndromes that are not addressed in the CPGs identified. In particular, we identified only one CPG for infants and none for the elderly. The results of this study offer guidance for future studies examining gaps in epilepsy CPGs. A full analysis of the gaps in epilepsy CPGs (CPGs that are out of date, of poor quality, or missing for high priority clinical areas) is needed, and should include consensus among epilepsy experts.

Our study is not without limitations. As discussed, considerable heterogeneity exists in the terminology and definition of CPGs. Our inclusion criteria were based on a commonly used, and standard, definition of a CPG,[1,2] and it is possible that some CPGs were missed. Still, considerable effort was made to ensure that all CPGs meeting inclusion criteria were identified through the use of a broad search strategy, hand-searching, and seeking input from experts in the field. Similarly, many guidelines developed and used at the local level may have been missed due to publication bias. The members of the ILAE Task Force on Epilepsy Guidelines along with the chairs of the ILAE commissions and task forces were surveyed to identify any CPGs developed within their local ILAE chapter or region, to increase the likelihood of identifying CPGs that may have been missed using our search strategy. None of these additional local "guidelines" identified by ILAE chapter members met our inclusion criteria. In addition, the scope of this systematic review was on the management and clinical care of persons with epilepsy, rather than the technical aspects of care, such as diagnostic tests (e.g., electroencephalography).

In conclusion, this study provides a comprehensive list of CPGs that address medical care of persons with epilepsy, which can be a useful resource for health professionals managing persons with epilepsy. Our findings also provide the groundwork for future studies aimed at: (1) identifying high priority areas where CPGs are needed, (2) creating standardized and rigorous CPG development methodology, and (3) developing effective implementation strategies. Such future studies have the potential to make great strides in improving the quality of care persons with epilepsy receive.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. The search strategy used for the systematic review.

Appendix S2. References for the included CPGs.

Figure S1. Forest plot of the quality portion of the included CPGs.