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Review

A systematic review of clinical decision rules for epilepsy

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ABSTRACT

Clinical decision rules (CDRs) have been empirically demonstrated to improve patient satisfaction and enhance cost-effective care. The use of CDRs has not yet been robustly explored for epilepsy. We performed a systematic review of MEDLINE (from 1946) and Embase (from 1947) using Medical Subject Headings and keywords related to CDRs and epilepsy. We included original research of any language deriving, validating, or implementing a CDR using standardized definitions. Study quality was determined using a modified version of previously published criteria. A bivariate model was used to meta-analyze studies undergoing sequential derivation and validation studies. Of 2445 unique articles, 5 were determined to be relevant to this review. Three were derivation studies (three diagnostic and one therapeutic), one validation study, and one combined derivation and validation study. No implementation studies were identified. Study quality varied but was primarily of a moderate level. Two CDRs were validated and, thus, able to be meta-analyzed. Although initial measures of accuracy were high (sensitivity ~80% or above), they tended to diminish significantly in the validation studies. The pooled estimates of sensitivity and specificity both exhibited wide 95% confidence and prediction intervals that may limit their utility in routine practice. Despite the advances in therapeutic and diagnostic interventions for epilepsy, few CDRs have been developed to guide their use. Future CDRs should address common clinical scenarios such as efficient use of diagnostic tools and optimal clinical treatment decisions. Given their potential for advancing efficient, evidence-based, patient-centered healthcare, CDR development should be a priority in epilepsy.

1. Introduction

Epilepsy is the second most common neurological condition seen in primary practice worldwide [1] with an approximate prevalence of 5.8 per 1000 population in the developed world and between 10.3 per 1000 to 15.4 per 1000 in developing countries [2]. Despite its prevalence, epilepsy can be very challenging to diagnose and treat. As such, it is not surprising that the annual cost of epilepsy in the United States was estimated at $12.5 billion in 2000 [3]. Mechanisms designed to optimize diagnostic and therapeutic decisions will be expected to reduce these costs. An accurate diagnosis and appropriate approach to treatment is crucial; it improves patient outcome, avoids exposing patients to potentially harmful treatment, and promotes efficient use of health-care resources.

The growing diagnostic and therapeutic options can be overwhelming for physicians and costly for the health-care system. For instance, there is evidence that electroencephalograms (EEGs) are overutilized by nonspecialists [4] while appropriate selection of patients for MRI would promote cost-effective care as up to 31% of people with epilepsy lack an obvious epileptogenic lesion on imaging [5]. The list of antiepileptic drugs (AEDs) is also growing, and choosing the correct one for each patient can be challenging [6].

Clinical decision rules (CDRs) are a way in which we can achieve these diagnostic and therapeutic goals. A CDR is used to quantify the individual contribution that multiple components of a patient's history, physical exam, laboratory, and/or imaging results make towards the likelihood of a certain diagnosis or response to treatment [7]. They have been empirically demonstrated to reduce inefficient provision of resources and prevent unnecessary exposure to risk when applied appropriately in the right clinical setting [8]. These rules offer advantages over simple decision analyses and clinical guidelines in that they empirically identify a discrete, unique course of action.

Clinical decision rules have been used with considerable success in other medical disciplines. These tools have proliferated over the last 20 years, and the number of scientific articles addressing the issue has

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more than doubled between 1995 and 2005 [9]. These have mainly been derived for acute clinical conditions encountered in emergency medicine [10–12], internal medicine [13,14], and surgery [15,16]. For the most part, these rules have achieved a sensitivity of 100% — a measure that elevates confidence in ruling out a condition and, thus, promotes uptake [10,11]. With the exception of stroke, few have been developed for neurology. However, scores such as the CHA_2DS_2-VASc [17] and HAS-BLED [18] have revolutionized the approach to prescribing antithrombotics for stroke prevention in nonvalvular atrial fibrillation. It is anticipated that CDRs that address the correct clinical questions with high sensitivity and specificity could improve care in epilepsy in a similar fashion by streamlining decisions about the use of adjunct diagnostic tests and guiding the use of AEDs according to a patient's risk profile.

The role of CDRs in epilepsy has yet to be explored. The purpose of this study was to systematically review the literature to critically appraise the use of CDRs in epilepsy.

2. Material and methods

2.1. Definitions

We defined a CDR as a rule that incorporates at least three variables from the history, physical examination, and/or diagnostic tests that provide a probability of an outcome and suggests a single diagnostic or therapeutic course of action [19]. These rules must not simply be survival analyses or prognostic models but must incorporate a decision rule that is used to empirically identify a unique course of action according to a patient's particular attributes [19].

2.2. Search strategy and selection criteria

The review was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20]. Methods of the analysis and inclusion criteria were specified in advance and documented in an unpublished protocol.

We searched Medline (from 1946) and Embase (from 1947) using a comprehensive search strategy that incorporated Medical Subject Heading (MeSH) and text words for CDRs (Appendix 1; most recent search date: July 2015). We also reviewed relevant studies identified in the reference sections of included articles.

We included studies containing original research, irrespective of patient age, language, or location, which derived a CDR. Decision analyses and practice guidelines were excluded from this review since they do not provide a discrete, single course of action. Rather, they evaluate many potential decision nodes factoring in a variety of costs and benefits. Thus, many potential options are available to the physician. On the other hand, CDRs provide a score that offers an explicit, singular course of action for a distinct and highly specific clinical question, thus, removing a level of uncertainty.

2.3. Study selection and data collection

Two authors (CBJ and SS) performed the literature search and screened study titles and abstracts. Both authors screened each abstract, and eligible articles were selected for full review. Full texts were reviewed in duplicate (CBJ and SS) to identify those that met eligibility criteria. Any disagreement was resolved by reaching consensus through discussion that included a senior author (NJ and SW) where necessary.

2.4. Data extraction

Variables extracted included year of publication, the country in which the study was conducted, inclusion criteria, participant recruitment (prospective, retrospective, both, or an administrative database), study setting (tertiary, secondary, or primary care), and the number of participants. The study design (whether it was a derivation, validation, or implementation study) and the study aim (diagnostic, therapeutic, or prognostic) were also documented.

A standardized mechanism for evaluating study quality is currently being developed (http://www.equator-network.org/resource-centre/library-of-health-research-reporting/reporting-guidelines-under-development/#3). In the absence of such a tool, we adapted previously proposed criteria [7,19] and applied them to all included studies (Appendix 2). Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) criteria [21], designed to evaluate the risk of bias in diagnostic studies,were also included because the process for establishing risk categories for individual patients closely approximates studies of diagnostic quality. The QUADAS-2 criteria involve a qualitative assessment without any attempt at creating a categorical index of study quality. Study quality was evaluated and tabulated for all included studies; studies were not excluded according to their overall quality level. Rather than using a quantitative scale, our tool was used to simply identify sources of bias for evaluative purposes.

Attempts were made to determine if study variables were identified *a priori*. The number of variables each study examined, including those that were not statistically significant, was tabulated. The type of statistical model used to derive the rule was documented along with the overall strength of prediction.

We followed the CDRs forward to determine if they underwent validation or implementation analyses through hand searching reference lists of included studies and through Google Scholar. When evaluating validation studies, we recorded whether additional variables were examined in an effort to refine the rule. We recorded the overall predictive strength of the rule in the new population and tabulated accuracy of use of the rule and measures of interobserver agreement.

2.5. Statistical analysis

We performed meta-analyses using RevMan5.2.3 [22] and Stata version 13.0 [23]. The bivariate meta-analytic method [24] was used to pool the study-specific sensitivity and specificity values since CDRs are designed using discrete thresholds [19]. We assessed statistical heterogeneity between studies within the bivariate model (by evaluating the prediction regions) [24] and explored publication bias using visual inspection of a funnel plot.

3. Results

3.1. Literature search

A Medline and Embase search in July 2015 yielded 2858 articles of which 2445 were determined to be unique after deduplication. We excluded 2355 after initial abstract review and a further 23 after consensus review. These were all excluded on the basis of being review articles or because there was no appended CDR. Sixty-two additional studies were excluded after full-text review leaving 5 studies (three derivation, one combined derivation and validation, and one validation) for the systematic review (e-Fig. 1) [25–29]. All studies were derived in high-income countries (2 in Europe, 2 in North America, and 1 in Australia).

3.2. Derived CDRs

The Frontal Lobe Epilepsies and Parasomnias (FLEP) scale [27,29] was derived from a pilot study of 18 cases by selecting variables from a literature search and clinical experience [29]. It was designed to guide diagnosis and treatment of patients with undifferentiated nocturnal events. No details are provided on this population or on how the model was assembled. Weights were arbitrarily applied to each variable following study of the pilot population. Ultimately, it was subsequently studied in a population of 62 patients both retrospectively and prospectively to determine diagnostic accuracy. This score was further validated