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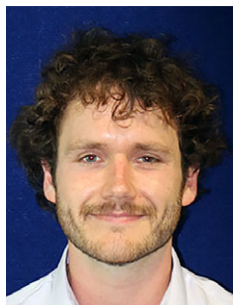
SHORT RESEARCH ARTICLE

Development of EpiRisk: An online clinical tool for estimating the risk of major congenital malformations in pregnant women treated for epilepsy

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Gabriel Davis Jones is a doctor of medicine and researcher with a keen interest in the application of bioinformatics, big data, and machine learning to healthcare.

SUMMARY

Antiepileptic drugs (AEDs) are known to associate with an increased risk of major congenital malformations (MCMs) in children born to women who become pregnant while taking them. As the indications for AEDs continue to diversify, novel AEDs emerge, and polytherapy becomes more prevalent, the volume and complexity of the information relating to teratogenic risk can become unmanageable for the clinician. This in turn makes accurate education of pregnant women treated with AEDs regarding the risk of MCMs challenging. To enable clinicians to provide better information regarding the potential teratogenic risk of AEDs, we outline here the method we have employed to underpin a new system of real-time risk analysis, “EpiRisk.” When launched, *EpiRisk* will offer a user-friendly, online clinical tool, compatible with all modern Internet browsers, smart phones, and personal computers. Using the most current published data, as well as “real world” data from the UK and the Australian Pregnancy Registers, *EpiRisk* will enable clinicians to quickly and accurately assess the teratogenic risk of AEDs in mono- and polytherapy. *EpiRisk* may thus provide a future-proof central hub for empowering patients, clinicians, and registries by delivering evidence-based information on the teratogenic risk of the AEDs in pregnant women with epilepsy through an easily accessible platform.

KEY WORDS: App, Antiepileptic drugs, Clinical tool, Epilepsy, Pregnancy, Teratogenicity.

Antiepileptic drugs (AEDs) are known to be associated with an increased risk of major congenital malformations (MCMs) in women who conceive while taking them.¹ However, most women with epilepsy who wish to become pregnant need to continue to take AEDs to protect against the serious risk of uncontrolled seizures to them, their unborn and born children, and others in the community. In

addition,, the number of women who are prescribed AEDs through pregnancy is increasing.² No longer restricted to the treatment of active epilepsy, AEDs are frequently utilized in a variety of indications, including migraines, psychiatric disorders, chronic pain, and sleep.^{3,4} As the indications for AEDs continue to diversify, the number of women taking these medications is increasing. Furthermore, novel AEDs

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are being licensed for clinical use, and polytherapy is becoming more prevalent.^{5,6} Therefore, sample sizes of individual studies reporting data on these drugs are limited in their power to analyze the effects of the newer drugs, and of the myriad of combinations of AEDs. This makes accurate education and counseling of women treated with AEDs challenging with respect to the risk of MCMs.

Herein we describe a novel methodology underpinning the current development of a suite of tools known as *EpiRisk*. The first clinical tool of its kind, *EpiRisk* will combine real-time clinical data through direct linkages with international pregnancy registers with peer-reviewed publications to provide a collaborative information platform to estimate teratogenic risk of AEDs in both mono- and polytherapy, allowing clinicians easy access to accurate data with which to inform their patients.

METHODS AND RESULTS

Data collection

The backbone of *EpiRisk* is literature published on the PubMed database. The source database was restricted to PubMed because the *EpiRisk* system will query and retrieve publication metadata from this database. This decision was made because of PubMed's well-documented application programming interface (API), which allows for efficient and robust querying via the ENTREZ programming utilities.

Once live, the initial setup of the *EpiRisk* system requires an administrator to enter the AEDs, select publications found through PubMed, and then manually confirm the entry of the related datasets. This also applies to register-specific datasets. The administrator will do this for each currently available medication. Once these AEDs, publications, and datasets have been entered into the system, they are stored there permanently, that is, this step is required only once. The *EpiRisk* system is then designed to automatically and continuously search for new publications for each entered drug without user input. When it finds potential valid publications (ie, newly published studies) it suggests these publications to the administrator, who is then able to accept or reject the entry of the new dataset into the backend of the system. The Australian and the UK and Ireland Pregnancy Registries are part of this project, and as new data emerge from these registries, such data will be highlighted to administrators who can incorporate these into the *EpiRisk* App.

To test the utility of *EpiRisk*, we performed a proof-of-concept study. Original publications were found through a PubMed search with the keywords "epilepsy," "pregnancy," and "polytherapy" in either the title or abstract published in the last 20 years. The publications selected for contribution to the model adhered to predetermined inclusion and exclusion criteria (Table S1), including papers reporting data on the number or the rate of MCMs observed for women with epilepsy (WWE) who are prescribed an AED. Studies that

reported on participant data for which there was a newer version of the same dataset available were excluded, as were articles that did not include data on total sample sizes or that did not contain a usable comparison group. In addition, reports that examined outcomes other than physical MCMs detectable in the first year of life (eg, developmental delay) were excluded, as were those that examined only 1 or 2 types of MCMs (eg, oral clefts). This was done due to a paucity of studies reporting on a limited number of birth defects as well as to avoid incorporating data into statistical analysis that could potentially increase the apparent risk of a single defect while simultaneously seeming to decrease the risk of other potential MCMs, thereby skewing analysis when reporting on the risk of any MCM given a certain combination of AEDs.

Analytical model development

A proof-of-concept model was created to demonstrate the statistical methodology and output for a risk model concerned with MCM risk and AEDs. The proof-of-concept model was focused on a single calculation of relative risk: the relative risk of a child being born with an MCM to a woman with epilepsy who was taking valproate monotherapy (VPA), compared to the risk for a woman with epilepsy not being treated with an AED for the duration of her pregnancy. We used the Cochran-Mantel-Haenszel method to perform the pooled analysis, as this is frequently used to pool results from clinical trials where studies are conducted across multiple centers and the variance between study groups is low. Furthermore, the organization of strata in this method allows for prompt integration of data from a multitude of publications. Results of individual studies are weighted according to the inverse of their variance, so that larger studies with smaller variance have a larger weight than smaller studies with larger variance.

Although a multitude of studies reporting on the prevalence of MCMs in pregnant women treated for epilepsy have been published, most of these were not appropriate for risk modeling. Studies were excluded from the proof-of-concept model because of the following: (1) they were updated versions of earlier reports; (2) they included results from earlier reports (thus gathering the results from both versions of the report results in a double-counting (or more) of certain results); (3) they failed to include an appropriate control group (eg, women with epilepsy not treated with an AED); or (4) they reported results similarly (exact number of women in study and number of MCMs, as opposed to aggregate rates). Ultimately, 4 studies were used in the proof-of-concept model representing the most recent data from 4 registers: North American AED Pregnancy Registry, Australian Pregnancy Register, UK Epilepsy and Pregnancy Register, and the National Medical Birth Registry of Finland.^{1,7-9}

The statistical analysis program *R* was used to calculate the relative risk ratio and confidence intervals using the

Cochran-Mantel-Haenszel method outlined. The results were then used to generate a forest plot of the newly derived risk ratio (Figure 1). For this proof-of-concept model, the relative risk of having a baby with an MCM is 3.98 times higher ($p < 0.001$) for a woman with epilepsy who is taking VPA compared to a woman with epilepsy who is not taking an AED. The 95% CI is 2.77 to 5.7. We thereby demonstrate that the algorithms underpinning *EpiRisk* can create a relative risk model with an associated CI for groups of studies, providing these studies are comparable, and do not “over-count” results. With this methodology, the *EpiRisk* system can perform analyses for single AEDs, but also for every drug and dose combination for which reliable data are available in the literature.

Web application development

The *EpiRisk* web application will be built using the Django web framework and Twitter Bootstrap packages, as each package has cross-platform mobility, simple implementation, and an established support base. A set of independent *SQLite* databases are used to store the *EpiRisk* data: a publication library, therapy library, dose library, study database, and outcome library (Figure 2). This allows for myriad simultaneous relationships between datasets while keeping each dataset separate. The *EpiRisk* functions, which are divided into front-end and backend functions, are built using JavaScript.

Front-end functions

Front-end functions comprise the suite of easily accessible clinical components that end-users (clinicians) can employ to perform real-time analysis with the Cochran-Mantel-Haenszel statistical method, data visualization in

the form of forest plots, a therapy library in which users can access a summary of contributing studies and statistics, *epiRegister* (an automated region-specific promotional function for recruiting patients into local pregnancy registries), and a therapy monitor for monitoring any literature updates in all therapies contributing to the *EpiRisk* system. Relative risk calculation outputs will be accompanied by the contributing values from each publication/register and totals for control and comparison groups.

Back-end functions

Back-end functions are those that serve an administrative purpose and can be accessed only by administrators of the *EpiRisk* system. To construct the initial *EpiRisk* system, the administrators enter keywords related to a specific AED and MCMs. These keywords are then parsed through the ENTREZ programming utility, and relevant publications are returned for the administrator to select based on inclusion and exclusion criteria (Table S1). Selected publications are then checked for duplication, and if the selected publications have not yet been entered into the databases, data from these selected publications are then parsed into their respective databases (Figure 2) and weighted accordingly (see Analytical Model Development). This function is then able to run independently at a frequency determined by the administrator such that new publications can be found without requiring manual entry. These new publications are then held until the administrator confirms their integration into the system. Once integrated, metadata from the publication as well as keywords found within the publication are parsed through a machine-learning function that utilizes these data to improve the efficiency and

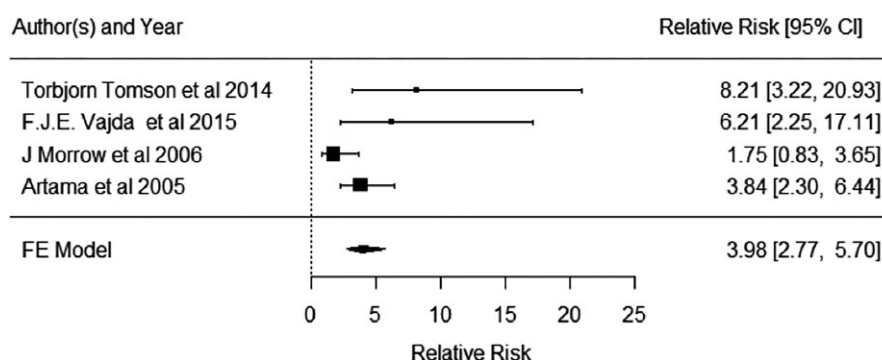
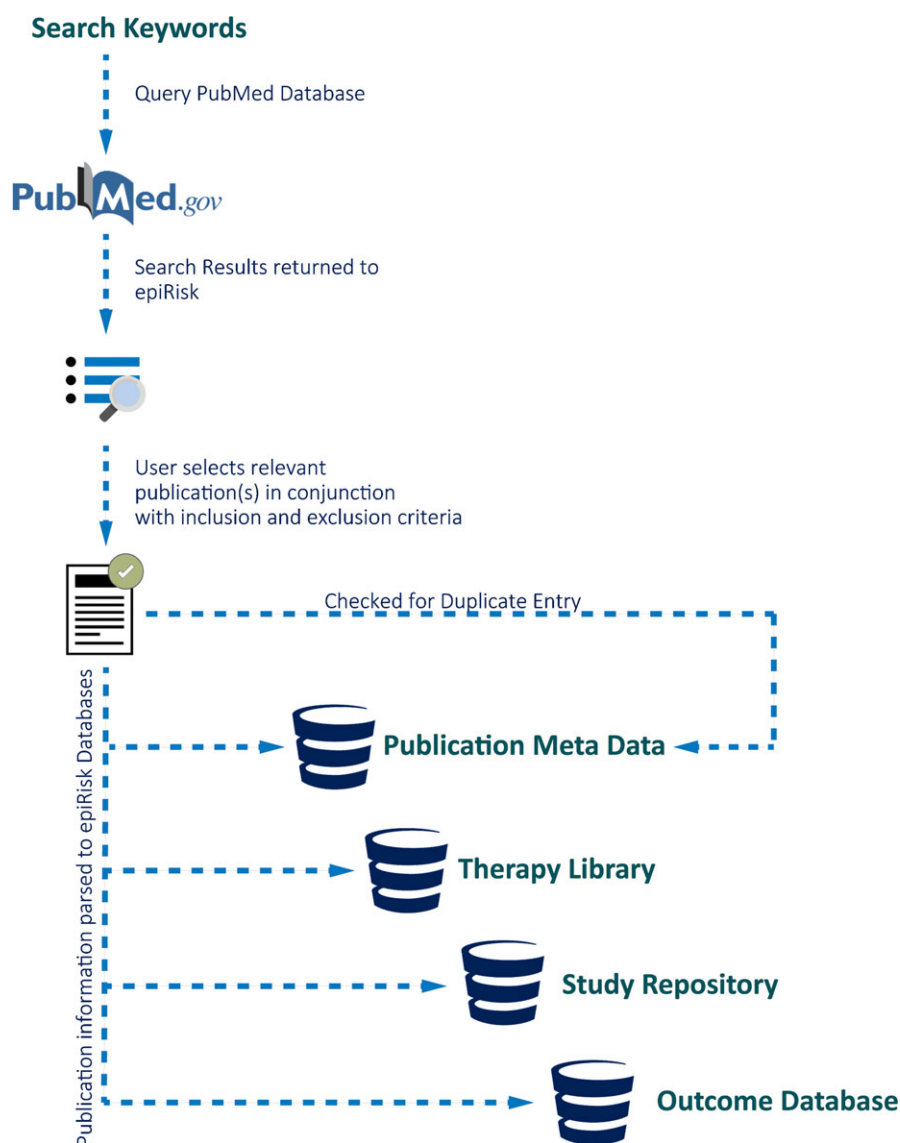


Figure 1.

Output of the *EpiRisk* Clinical Tool with the Sodium Valproate Monotherapy (VPA) Proof of Concept Model. The complete output comprises a forest plot and the calculated risk ratio. The Cochran-Mantel-Haenszel statistical method was employed using statistical analysis software package R Studio to perform analysis and generate subsequent forest plots. Included studies are listed alongside the reported relative risk ratios provided by each publication. The fixed-effect modeling risk ratio output is then displayed below alongside the risk ratio with confidence intervals. The total number of included samples was 3364 (765⁷, 455⁸, 942¹, and 1202⁹, respectively). A total of 1573 women were included in the VPA monotherapy treatment group. Pregnant women with epilepsy who were not being treated with any AED while pregnant comprised the control group, which included 1791 women.

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**Figure 2.**

Building the *EpiRisk* system pipeline. In the initial setup phase, the *EpiRisk* database is first constructed when the administrator enters search keywords that then query the PubMed database via the ENTREZ API. Publication search results are returned to the *EpiRisk* system. The administrator selects which publication(s) will enter the *EpiRisk* databases. Metadata from the selected publications are then retrieved and checked against the *EpiRisk* databases to prevent duplicate entries. The publication information is then split into the respective *EpiRisk* databases: Publication Meta Data, Therapy Library, Study Repository, and Outcome Database. When an end-user queries an AED combination, the relevant studies and outcomes are retrieved from the database. The relative risk ratio and confidence intervals using the Cochran-Mantel-Haenszel method are then derived. These risk ratios are plotted on a forest plot and displayed alongside the pooled relative risk ratio, confidence interval (CI) upper bound, and CI lower bound. In addition, based on the user's geographic location, the appropriate epilepsy in the pregnancy register is promoted with the provision of a link, promoting the enrollment of the patient into the register.

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specificity with which potential publications are found in the PubMed database. Through a separate pipeline that allows for entry of numbers, rates, and types of MCMs in pregnant women currently being treated for epilepsy, administrators can enter real-world data from epilepsy and pregnancy registries into the system. These databases

are the same databases that are utilized in front-end functions and thus provide real-time values for relative-risk calculation. The time requirement for administration of the *EpiRisk* system is minimal, requiring a few hours per week; however, this requirement will decline as the machine learning functionality becomes more efficient.

DISCUSSION

To enable clinicians to provide readily accessible and more accurate information regarding the potential teratogenic risk of AEDs, we have developed the methodology to build “*EpiRisk*”: an online clinical tool compatible with all modern Internet browsers, smart phones, and personal computers that serves as a repository for calculating the risk of MCMs in pregnant women who are being treated for active epilepsy. Using the most current published data, as well as “real world” data from the UK and Ireland and the Australian Pregnancy Registers, *EpiRisk* will enable clinicians to quickly and accurately assess the risk of the teratogenic side effects of AEDs in mono- and polytherapy for any combination of AEDs entered into the *EpiRisk* databases.

Epilepsy and pregnancy registers can connect to *EpiRisk* for automatic promotion to users based on geographic location, thereby enhancing registration of more pregnant women taking AEDs, which, in turn, will continuously improve the data on the risks that AEDs may pose in pregnancy. As *EpiRisk* gains traction, we would look to collect long-term developmental data on children who have been exposed to AEDs in utero and thereby further inform the data that *EpiRisk* provides in an iterative process. These new data are critically needed for the newer AEDs, and the multitude of combinations of AEDs that are now used in pregnant women.

CONCLUSION

We have developed methodology to underpin the first online clinical tool to accurately estimate the risk of single and combination AED therapy, enabling clinicians to better inform women who are contemplating pregnancy of the risks associated with their specific treatment regimen. Having tested *EpiRisk* in a proof-of-concept study, we are now adding available datasets regarding mono- and polytherapy regimens to the platform. *EpiRisk* also allows clinicians to better encourage women to register with local pregnancy registries and provides easy access to the original literature and data, ensuring complete transparency relating to the risk estimates provided. The highly adaptable nature of the *EpiRisk* platform will, in due course, allow for rapid

integration, not only with other areas of neurology, but also in a multitude of medical specialties. We plan to launch the *EpiRisk* App as a worldwide free download in 2018.

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DISCLOSURE

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. Inclusion and exclusion criteria that a publication must pass to enter the *EpiRisk* system.