TITLE: The incidence and prevalence of drug resistant epilepsy: A systematic review and meta-analysis

AUTHORS

Bushra Sultana MD,[1,2] Marie-Andrée Panzini MD,[1,2] Ariane Veilleux Carpentier MD,[1,2] Jacynthe Comtois MD FRCPC,[1,2] Bastien Rioux MD,[1,2] Geneviève Gore MLIS,[3] Prisca R Bauer MD PhD,[4] Churl-Su Kwon MBBS MPH FRSPH,[5] Nathalie Jetté MD MSc FRCPC,[5,6] Colin B Josephson MD MSc FRCPC,[6] Mark R Keezer MDCM PhD[1,2,7]

[1.] Research Centre of the Centre Hospitalier de l'Université de Montréal (CRCHUM), Canada

[2.] Department of Neurosciences, Université de Montréal, Canada

[3.] Schulich Library of Physical Sciences, Life Sciences, and Engineering, McGill University, Canada

[4.] Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Freiburg, Germany

[5.] Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, USA

[6.] Department of Clinical Neurosciences and Hotchkiss Brain Institute, University of Calgary, Canada

[7.] School of Public Health of the Université de Montréal, Canada.

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CORRESPONDING AUTHOR:

Mark R Keezer

Centre Hospitalier de l'Université de Montréal

Pavillon R R04-700

1000, rue Saint-Denis

Montréal, QC, H2X 0C1, Canada

phone: +01 514 890 8233

email: mark.keezer@umontreal.ca

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All authors contributed to the design of the study protocol. GG designed and executed the search of electronic databases. BS, MAP, PB, AVC, JC, NJ, CBJ, CSK, BR, and MRK carried out the systematic review. MRK carried out the statistical analyses. BS and MRK drafted the manuscript. All authors critically revised the manuscript.

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ABSTRACT

Objective: In order to evaluate the incidence and prevalence of drug-resistant epilepsy (DRE) as well as its predictors and correlates, we conducted a systematic review and meta-analysis of observational studies.

Methods: Our protocol was registered with PROSPERO and the PRISMA and MOOSE reporting standards were followed. We searched MEDLINE, Embase, and Web of Science. We used a double arcsine transformation and random-effects models to carry out our meta-analyses. We performed random-effects meta-regressions using study-level data.

Results: Our search strategy identified 10,794 abstracts. Of these, 103 articles met our eligibility criteria. There was high inter-study heterogeneity and risk of bias. The cumulative incidence of DRE was 25.0 % (95% CI: 16.8, 34.3) in child studies but 14.6% (95% CI: 8.8, 21.6) in adult/mixed ages studies. The prevalence of DRE was 13.7% (95% CI: 9.2, 19.0) in population/community-based populations but 36.3% (95% CI: 30.4, 42.4) in clinic-based cohorts. Meta-regression confirmed that the prevalence of DRE was higher in clinic-based populations and in focal epilepsy. Multiple predictors and correlates of DRE were identified. The most reported of these were having a neurological deficit, an abnormal EEG, and symptomatic epilepsy. The most reported genetic predictors of DRE were polymorphisms of the *ABCB1* gene.

Conclusions: Our observations provide a basis for estimating the incidence and prevalence of DRE, which vary between populations. We identified numerous putative DRE predictors and correlates. These findings are important to plan epilepsy services, including epilepsy surgery, a crucial treatment option for people with disabling seizures and DRE.

INTRODUCTION

Epilepsy affects almost 1.0% of the general population.[1] Many people with epilepsy respond to antiseizure medications (ASMs) and become seizure-free.[2] Some people, however, continue to have seizures despite optimal pharmacological therapy.[3] The International League Against Epilepsy (ILAE) defines drug resistant epilepsy (DRE) as the "failure of adequate trials of two tolerated, appropriately chosen and used AED (*sic*) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom."[4]

Recognizing DRE is important. Seizure frequency is a major determinant of quality of life, as well as healthcare use and cost.[5, 6] Randomized controlled trials in adults and children, along with more than one hundred observational studies and case series, demonstrate that resective epilepsy surgery is highly efficacious in rendering individuals with DRE seizure-free.[7, 8, 9, 10]

There remains variability in the reported likelihood that a person with epilepsy will fail to sufficiently respond to ASMs. Part of this relates to inconsistencies in the definition of DRE. The cumulative incidence of DRE in one population of children with epilepsy was as low as 9% or as high as 24%, depending on the DRE definition used.[11] Uncertainty also remains on how the incidence and prevalence of DRE may vary between different populations[12, 13] and what may be predictors of drug resistance.[13, 14, 15]

The present systematic review and meta-analysis aims to exhaustively examine the incidence and prevalence of DRE in people with epilepsy. We will explore how DRE incidence and prevalence vary between populations. We will examine for factors associated with DRE in populations at risk.

METHODS

This is a systematic review and meta-analysis of observational studies. We developed an *a priori* protocol and completed this report according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, as well as those of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group and the Ottawa Non-Randomized Studies Workshop.[16, 17, 18] The finalized study protocol was registered with the PROSPERO international prospective register of systematic reviews prior to the initial review of the titles and abstracts (https://www.crd.york.ac.uk/PROSPERO/; registration number: CRD42016051814).

Eligibility criteria

All studies reporting the incidence (cumulative or density) or prevalence (point, period, or lifetime) of DRE in people with epilepsy were considered eligible for inclusion in this systematic review. We also included studies that reported factors associated with DRE including predictors (longitudinal incidence or case-control studies) and correlates (cross-sectional prevalence studies) of DRE among individuals at risk. We included published and unpublished studies in any language of publication. We considered studies that collected data prospectively or retrospectively. Though we did not limit eligibility by any one definition of DRE, we only included studies that defined it relative to the use of ASMs (i.e. excluding studies that studied epilepsy remission without considering the number of unsuccessful ASM trials).

When necessary, professional colleagues fluent in the appropriate language translated an article into English. We limited our search to articles published after 1970. Second generation ASMs were not available prior to 1970 and therefore the availability and clinicians' understanding of syndrome-appropriate ASMs would not have matched modern standards.

We defined epilepsy as a history of two or more unprovoked epileptic seizures separated by at least 24 hours.[19] More recently, the ILAE adopted an expanded definition of epilepsy.[20] Our initial protocol sought to exclude studies that used this newer definition, expecting that large-scale population-based studies would not use it. Finally, after identifying three informative studies[21, 22, 23] that applied, at least in part, this newer definition, we chose to change this criterion and to include these studies.

If more than one study published estimates based upon the same participants, only the more complete study was included to not over-represent particular data, unless the different articles provided data on different outcomes.

Search strategy

We designed the search strategy of electronic databases in consultation with a life sciences librarian with expertise in knowledge synthesis (GG). We also sought input from epilepsy experts (NJ, MRK). We searched the following electronic databases: Ovid MEDLINE (1970 to 2020), Ovid EMBASE (1970 to 2020), and Web of Science CPCI-S (1970 to 2020). The initial search was conducted on 14 November 2016 and updated on 1 April 2020. The final search strategy is presented in Table 1.

We manually searched the bibliographies of included articles for additional relevant studies. We also manually searched the 2015 to 2020 proceedings of the annual meetings of the American Epilepsy Society, the American Academy of Neurology, the European Congress on Epileptology, and the International Epilepsy Congress.

Study selection

Each title and abstract identified by the initial search were independently screened by two reviewers (BS, CBJ, NJ, or MRK). We obtained the full text of an article if either reviewer suspected that it was possibly relevant to our research questions. Two reviewers (BS, MAP, BR, or MRK) independently evaluated all full-text articles. Any disagreements on study eligibility between the reviewers were settled by consensus, with the help of a third reviewer when necessary (MRK or NJ). Study eligibility was not influenced by the subsequent risk of bias assessment.

Data extraction

For each study, data were independently extracted by two reviewers (BS, MAP, PRB, AVC, JC, CBJ, CSK, or MRK). A data extraction form was specifically designed for this study. It was piloted on five studies, after which we made final adjustments to improve its usability. In studies that did not clarify a specific definition of DRE but rather described the response to a series of ASMs, we imposed a definition of DRE that matched the ILAE definition as closely as possible.[24] We classified a study as an adult study if at least 80% of participants were at least 16 years old. We classified a study as a child study if at least 80% of participants were less than 16 years old. If a primary study did not fulfill either of these criteria, it was classified as mixed ages.

Assessment of risk of bias

The risk of bias of each included study was independently assessed by two reviewers (BS, MAP, PRB, AVC, JC, CBJ, CSK, or MRK). We used a quality assessment instrument specifically designed for this review [data available from Dryad (Table e-2): https://doi.org/10.5061/dryad.6t1g1jwxd], whose design was based upon the recommendations of

the Ottawa Non-Randomized Studies Workshop and MOOSE guidelines.[17, 25] The quality assessment instrument was initially piloted on five studies, after which adjustments were made.

Data synthesis and analysis

We synthesized and analyzed aggregate, study-level data. We used the Wilson method to calculate 95% confidence intervals (CI) for the incidence and prevalence parameters.[26] We conservatively assumed that each primary study estimate reflected a different parameter for a particular source population. We therefore used a random-effects model to calculate the pooled incidence and prevalence estimates and associated 95% CI, as has been recommended by the Ottawa Non-Randomized Studies Workshop.[27] We used a double arcsine transformation to stabilize variances, as recommended for the meta-analysis of incidence and prevalence data.[28] For the effect measures examining predictors or correlates of DRE, we chose not to perform meta-analyses due to concerns regarding the heterogeneity in the way the variables were defined and measured.

We visually inspected forest plots and calculated I^2 statistics to assess the degree of inter-study heterogeneity.[29] We investigated possible sources of heterogeneity by subgroup analyses. The stratifying variables were: clinic-based cohorts versus population/community-based cohorts, adult/mixed ages versus child studies, epilepsy type (e.g. generalized versus focal epilepsy), period versus point prevalence, and primary studies that used the ILAE-supported definition of DRE [4] versus those studies that did not use this definition. Our protocol had initially specified subgroup analyses by epilepsy etiology but this was changed to epilepsy type based upon the availability of data.

We further studied sources of heterogeneity using random-effects meta-regression.[30] This method allows for the inclusion of study-level variables to model the relationship between an outcome variable (incidence and prevalence in the context of this review) with multiple explanatory variables, both categorical and continuous. Incidence and prevalence were not log-transformed, as recommended by the Cochrane Collaboration, given that they are not ratio estimates.[31] The explanatory variables included in each meta-regression model were the same as those used for stratification, with the addition of year of publication (as a continuous variable).

We evaluated reporting bias (including publication bias) by visual inspection of funnel plots. We did not employ other formal tests to measure the degree of reporting bias as these are not validated in observational studies. As has been previously recommended, however, we assumed that the risk of publication bias among observational studies is high.[17, 32]

We organized references using Distiller Systematic Review (SR) software (Evidence Partners, Ottawa, Ontario, Canada). We used STATA/SE, version 14.0 (StataCorp LP, College Station, Texas, USA) to conduct all statistical analyses.

RESULTS

Included studies

Our initial electronic database search strategy identified 10,794 titles and abstracts. The review of these, along with articles identified through manual searching, resulted in 103 articles included in our systematic review. The reasons for excluding full text articles are summarized in the PRISMA flow diagram (Figure 1). The included studies amassed a total of 9,059 participants in incidence studies (n = 24) and 1,479, 385 participants (1,376,756 participants accounted for by

one study)[33] in prevalence studies (n = 59). The basic characteristics of these studies are available from Dryad (Table e-1): https://doi.org/10.5061/dryad.6t1g1jwxd. The risk of bias was high for many studies, for all aspects examined, including representativeness of the sample, data collection, case-ascertainment, and statistical analyses [data available from Dryad (Table e-2): https://doi.org/10.5061/dryad.6t1g1jwxd]. Twenty-two studies used a case-control design and therefore did not report a valid incidence or prevalence estimate.

Incidence of DRE

The overall pooled cumulative incidence across all 24 studies was 19.6% (95% CI: 14.4, 25.4) (Figure 2). Stratified analyses showed a trend towards a higher pooled incidence in studies of children versus adult/mixed ages [25.0% (95% CI: 16.8, 34.3) versus 14.6% (95% CI: 8.8, 21.6), respectively] (Figure 2C).

Eighteen incidence studies reported follow-up periods of at least 2 years, some as many as 42 years [data available from Dryad (Table e-1): https://doi.org/10.5061/dryad.6t1g1jwxd]. Only one study reported cumulative incidence with a follow-up period shorter than one year, with some participants followed for only two months; it is worth noting that this study reported one of the highest cumulative incidence amongst identified studies.[34] Ordering the studies by year of publication did not reveal a consistent change in reported incidence over time (Figure 2B). Meta-regression did not prove any independent correlates of incidence reported by the primary studies (Table 2). The funnel plot for incidence studies did not reveal visually evident reporting bias (Figure 3A). There was significant heterogeneity between studies (I^2 = 97.7%, p-value < 0.001).

Prevalence of DRE

The overall pooled prevalence across 59 studies was 32.4% (95% CI: 28.1, 36.8) (Figure 4). Stratified analyses found that the prevalence among studies of population/community-based populations was less than half that of clinic-based populations [13.7% (95% CI: 9.2, 19.0) versus 36.3% (95% CI: 30.4, 42.4), respectively] (Figure 4). Stratified analyses also found that there was a trend for the definition of DRE used by studies to be associated with the prevalence estimate (ILAE definition, prevalence = 35.6 95% CI: 29.3, 42.2); non-ILAE definition, prevalence = 27.0% (95% CI: 22.6, 31.7)] but there remained some overlap in the 95% CI (Figure 4B). Meta-regression showed that after simultaneous adjustment for the six study-level variables, clinic-based study and focal epilepsy were significant predictors of prevalence [prevalence ratio = 1.22 (1.07, 1.39) and = 1.20 (1.05, 1.37), respectively] (Table 2).

Of the 59 prevalence studies, only five reported period prevalence while the remainder reported point prevalence. The type of prevalence did not have a significant effect on the average prevalence estimate reported by the primary study (Figure 5D). Ordering studies by year of publication did not reveal a consistent change in reported prevalence over time (Figure 5A). There was no evidence of reporting bias in the funnel plot of prevalence studies of clinic-based populations (Figure 3B), although the distribution of prevalence estimates was independent of study standard error (which is very dependent on sample size) suggesting that the major determinant of this distribution was the significant inter-study heterogeneity (I^2 = 99.8%, p-value < 0.001). There were only nine studies of prevalence in population/community-based studies therefore we did not construct a funnel plot for these, as prescribed by our protocol.

Predictors and correlates of DRE

We identified 83 studies that measured predictors or correlates of DRE. The full details for each study reporting predictors or correlates of DRE, and the strength of the associations, are available

from Dryad (Table e-3): https://doi.org/10.5061/dryad.6t1g1jwxd]. Table 3 summarizes these into six themes (demographics, clinical features, epilepsy treatment, epilepsy etiology, comorbidities, and genetic polymorphisms), and distinguishes between those found to be statistically significant in at least three studies versus those reported in fewer studies.

Among the clinical variables, we found that the most commonly reported predictors were having a neurological deficit, symptomatic epilepsy, and abnormalities on the EEG.

Nine of the 18 studies examining genetic determinants of DRE reported on polymorphisms of the *ABCB1* gene. Three polymorphisms (C345T , C1234T and G2677T) were evaluated and statistically significant results were found in six studies, while an additional three reported associations that were not statistically significant. All nine studies studied the C345T polymorphism of the *ABCB1* gene and the C1234T and G2677T polymorphism were evaluated in three studies each. It should be noted that there was significant heterogeneity in the study designs and the populations tested in these studies.

DISCUSSION

Our systematic review identified 103 studies examining the incidence, prevalence, or factors associated with DRE. The pooled cumulative incidence of DRE was 19.6% (95% CI: 14.4, 25.4). The pooled prevalence of DRE was 13.7% (95% CI: 9.2, 19.0) in population/community-based populations but 36.3% (95% CI: 30.4, 42.4) in clinic-based populations. In other words, our results show that on average, amongst those with new-onset epilepsy, approximately 20% will develop DRE at one point in time. A cross-sectional sample (i.e. including new-onset as well as chronic epilepsy but likely not those in remission) of population/community-based individuals

will on average find that 14% of individuals suffer from DRE (36% in a clinic-based population). Meta-regression showed that after adjusting for other study-level variables, clinic-based studies (vs population/community-based) and focal epilepsy studies (vs mixed or generalized epilepsy) were each associated with a 22% and 20% relative increase in the reported prevalence, respectively.

There are two prior systematic reviews on the frequency of drug resistance among people with epilepsy.[19, 20] Kalilani et al. identified 38 relevant studies and reported a pooled prevalence of 30% (95% CI: 19, 42) and a pooled incidence of 15% (95% CI: 11, 19).[35] These findings are difficult to compare to ours given that this prior review did not stratify primary studies into those studying a population/community-based cohort versus a clinic-based cohort. Our analyses show that this has a strong impact on the reported prevalence. Xue-Ping et al. identified 16 relevant studies and reported a pooled frequency of DRE of 25% (95% CI: 17, 32) although this estimate which was reported as a pooled prevalence was in fact based upon studies of incidence.[36] Our review identified many-fold greater number of relevant studies, used a double arcsine transformation when pooling incidence and prevalence data, as recommended,[28] and used meta-regression to comprehensively study sources of heterogeneity in the incidence and prevalence estimates reported by the primary studies.

There was significant heterogeneity in the reported incidence and prevalence estimates. As a result, our pooled estimates should be interpreted with caution. We used random effect models to pool these data, a method that better accommodates inter-study heterogeneity. Most importantly, we identified a number of potential sources of heterogeneity in the incidence and prevalence estimates, using stratified analyses and meta-regression. The trend towards a higher cumulative incidence in studies of children, as compared to adult/mixed ages, likely is related to differences

in epilepsy etiology as well as the fact that many studies of children excluded individuals with more "benign" epilepsy syndromes (e.g. benign rolandic epilepsy and/or childhood absence epilepsy). Study setting (e.g. clinic-based versus population/community-based) was a statistically significant and strong predictor of prevalence, associated with a 22% relative increase in the reported study prevalence, after adjustment. This is not surprising given that it is reasonable to assume that people with more severe/active forms of epilepsy are more likely to be followed in specialized medical clinics, resulting in strong selection bias in clinic-based studies.

We also found that focal epilepsy type (versus any or generalized epilepsy) is a significant predictor of DRE prevalence. Prior individual studies have been inconsistent, some showing an increased prevalence of DRE among people with focal epilepsy [37] while others, including population-based cohorts,[38] have not.

We did not identify the definition of DRE, even after adjustment for other potential predictors using meta-regression, as a great source of heterogeneity between studies. This is consistent with the findings of one prior systematic review of DRE.[35] Our inability to identify definition of DRE as a source of heterogeneity may be due to the overall heterogeneity between studies that mask this effect. Individual studies, nevertheless, have highlighted the possible impact of DRE definition. One prior study of children found a cumulative incidence of intractable epilepsy that varied between 9% and 24%, depending on the definition used.[11] The pivotal report on the longitudinal cohort followed at the Western Infirmary, Scotland, reported that 40% of people with new-onset epilepsy fail to respond to either of the first two ASM trials.[2] A subsequent analysis of this same clinic-based cohort reported a cumulative incidence of 12% once the ILAE definition of DRE was used.[39]

A strength of our study is the systematic and extensive search of the literature which identified 103 studies relevant to our research questions. As a result, we are able to provide more precise pooled estimates and were able to perform a great number of stratified analyses and construct meta-regression models to examine for sources of heterogeneity. Our methods were rigorous and transparent; our *a priori* protocol was published online with the PROSPERO international prospective register of systematic reviews.

It is important to recognize our study's limitations. The presented estimates of cumulative incidence may be underestimations given the sometimes short duration of follow-up reported in the primary studies. The important degree of inter-study heterogeneity emphasizes that although the pooled estimates that we report can be interpreted as weighted averages across studies, it is unlikely that there is one "true" incidence or prevalence for all populations. Rather, incidence and prevalence vary by study setting (e.g. population/community-based versus clinic-based) as well as other aspects (including, but not limited to, study design, epilepsy etiology, genetic susceptibility and comorbidities). The funnel plot for the prevalence data of clinic-based studies did not show the presence of reporting bias but was likely influenced by considerable heterogeneity. We could not use the trim-and-fill method, however, to calculate what a hypothetical pooled estimate would be in the absence of reporting bias given that this method has been previously shown to produce biased results in the presence of significant inter-study heterogeneity.[40]

We identified numerous predictors and correlates of DRE described in the scientific literature, including demographic and clinical features, epilepsy etiology, comorbidities, and genetic polymorphisms. Some of these variables may represent features inherent to a study's design or nuances of clinical practice, such as the association of a longer disease duration and DRE. Others

represent probable biological mechanisms of DRE, such as the reported genetic polymorphisms that are associated with the development of DRE. It is also worth noting that counting the number of studies that report a factor as statistically significant is imperfect and may not only reflect the biological importance of the factor but also the number of studies conducted in that particular subfield. The most frequently reported predictors and correlates of DRE included having a neurological deficit, an abnormal EEG and symptomatic epilepsy. These three factors point towards the idea that an underlying structural, infectious, immune or metabolic etiology of epilepsy, especially when it leads to neurological or electrophysiological abnormalities, are predictive of a more severe course of epilepsy. This is not an entirely novel concept but our findings offer objective evidence for this and lend support to the practice of completing a detailed imaging and EEG investigation from the beginning for each individual with epilepsy in order to identify earlier those at higher risk of developing DRE.

We also identified genetic variables associated with DRE. Of particular interest is the *ABCB1* gene, which encodes for an ATP-dependent cellular transporter named p-glycoprotein. It is found at the blood brain barrier in humans and is responsible for the efflux of xenobiotic compounds.[41] The transporter hypothesis of DRE suggests that p-glycoprotein could play a role in pharmacoresistance by decreasing the central nervous system uptake of ASMs. This was first postulated by a study demonstrating the overexpression of *ABCB1* mRNA in resected brain tissue from people with DRE.[42] While at this time the data are inconsistent regarding a definitive association between the *ABCB1* gene and DRE, and testing for ABCB1 polymorphisms is not generally available to most medical institutions, the findings are promising and could eventually be used to identify individuals who may benefit from future therapeutics using transporter inhibitors.[43]

There is a growing emphasis on predicting clinical outcomes in medicine, related to personalized medicine. Future studies should assess how different variables can be used together to accurately predict the risk of DRE for an individual. This could allow for more informed patient counseling and more-timely evaluations for epilepsy surgery.

Our review summarizes and analyses existing data on the incidence and prevalence of DRE. Our findings highlight that the risk of DRE is different depending on the setting, with a general population or community-based population at half the risk of a clinic-based population. These results will allow for the more efficient planning of future studies of DRE incidence and prevalence. These findings will also help inform the provision of epilepsy services, including epilepsy surgery, an important treatment option for people with disabling seizures and DRE. The literature emphasizes the probable underutilization of epilepsy surgery.[44] Properly understanding the current number of people with DRE is fundamental to understanding the degree of underutilization; our review greatly contributes to the study of these complex issues. Future studies should continue to examine what factors can explain heterogeneity in incidence and prevalence estimates including whether these frequencies are changing with the introduction of newer ASMs.

TABLES

Table 1: Electronic database search strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily <1946 to Present>

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1 exp epilepsy/
2 (epilep* or seizure* or infantile spasm* or convuls*).ti.
3 or/1-2
4 exp Drug Resistance/
5 (exp treatment failure/ or treatment outcome/) and recurrence/
6 (pharmacoresist* or refractory or drug resist* or medication resist* or therapy resist* or treatment resist*).ti.
7 (((drug or treatment) adj (fail* or response*)) or ((poor or treatment*) adj outcome*)).ti. (16267)
8 or/4-7
9 3 and 8
10 Drug Resistant Epilepsy/
11 ((pharmacoresist* or refractory or drug resist* or medication resist* or therapy resist* or treatment resist*) adj6 (epilep* or seizure* or infantile spasm* or convuls*)).ti,ab,kf.
12 or/9-11
13 epidemiologic methods/ or exp epidemiology/ or follow up studies/ or incidence/ or longitudinal studies/ or exp population/ or prevalence/ or prospectives studies/ or retrospective studies/
14 (community or epidemiolog* or follow* up or incidence or longitudinal* or population or prevalence or prospective* or retrospective*).ti,ab,kf.
15 13 or 14
16 12 and 15
17 16 not (exp animals/ not humans.sh.)

Ovid Embase Classic+Embase <1947 to 2016 November 14>

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1 exp *epilepsy/
2 (epilep* or seizure* or infantile spasm* or convuls*).ti.
3 or/1-2
4 *drug resistance/ or *multiple drug resistance/
5 exp *treatment failure/
6 *therapy resistance/
7 (pharmacoresist* or refractory or drug resist* or medication resist* or therapy resist* or treatment resist*).ti.
8 (((drug or treatment) adj (fail* or response*)) or ((poor or treatment*) adj outcome*)).ti. (21520)
9 or/4-8
10 3 and 9
11 drug resistant epilepsy/ or exp epilepsy/dr
12 ((pharmacoresist* or refractory or drug resist* or medication resist* or therapy resist* or treatment resist*) adj6 (epilep* or seizure* or infantile spasm* or convuls*)).tw.
13 or/10-12
14 community/ or epidemiology/ or follow up/ or incidence/ or longitudinal study/ or population/ or population research/ or prevalence/ or prospective study/ or retrospective study/
15 (community or epidemiolog* or follow* up or incidence or longitudinal* or population or prevalence or prospective* or retrospective*).tw.
16 14 or 15
17 13 and 16
18 17 not ((exp animal/ or nonhuman/) not exp human/)
19 limit 18 to yr="1970 -Current"
20 limit 19 to medline
21 19 not 20

Web of Science

# 1	TS=(epilep* or seizure* or "infantile spasm*" or convuls*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
# 2	TI=(((drug or treatment) NEAR/1 (fail* or response*)) or ((poor or treatment*) NEAR/1 outcome*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
# 3	TI=(pharmacoresist* or refractory or "drug resist*" or "medication resist*" OR "therapy resist*" OR "treatment resist*") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
# 4	#1 AND (#2 OR #3) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
# 5	TS=((pharmacoresist* or refractory or "drug resist*" or "medication resist*" OR "therapy resist*" OR "treatment resist*") NEAR/6 (epilep* or seizure* or “infantile spasm*” or convuls*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
# 6	#4 OR #5 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
# 7	TS=(community or epidemiolog* or “follow* up” or incidence or longitudinal* or population or prevalence or prospective* or retrospective*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
# 8	#6 AND #7 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1970-2016

Table 2: Meta-regression, predictors of the prevalence of drug resistant epilepsy

Adjusted incidence predictors (n = 24 studies)[¶]	**Incidence ratio (95% CI)**
Clinic-based studies (versus population- or community-based)	0.98 (0.85, 1.13); p=0.745
ILAE definition of DRE (versus non-ILAE definition)	0.92 (0.80, 1.06); p=0.258
Children (versus adult or mixed studies)	1.11 (0.99, 1.26); p=0.073
Year of publication	1.01 (1.00, 1.03); p=0.055
Adjusted prevalence predictors (n = 59 studies)[*]	**Prevalence ratio (95% CI)**
Clinic-based studies (versus population- or community-based)	1.22 (1.07, 1.39); p=0.005
Focal epilepsy (versus any type or generalized epilepsy)	1.20 (1.05, 1.37); p=0.007
ILAE definition of DRE (versus non-ILAE definition)	1.06 (0.93, 1.22); p=0.369
Children (versus adult or mixed studies)	0.99 (0.87, 1.12); p=0.883
Point prevalence (versus period prevalence)	1.05 (0.87, 1.27); p=0.593
Year of publication	1.01 (0.99, 1.02); p=0.334

CI: confidence interval; ILAE: International League Against Epilepsy; DRE: drug resistant epilepsy.

[¶] The four incidence predictors were included in the same meta-regression model.

[*] The five prevalence predictors were included in the same meta-regression model.

Table 3: Summary of predictors and correlates of drug resistant epilepsy

	Reported in ≥ 3 studies as statistically significant (number of studies)	**Reported in < 3 studies as statistically significant**
Demographics	• Younger age at onset (17) • Longer disease duration (3) • Female sex (3)	• Male sex • Alcohol or drug abuse • Employment status • Family history of epilepsy • Geographical region of residence • Level of activity within the medical system • Personal mobile phone use
Clinical features	• Abnormal EEG (epileptic as well as other abnormalities) (11) • High baseline seizure frequency (10) • Multiple seizure types (8) • Seizure type (in particular focal) (6) • Status epilepticus (6)	• Atonic, tonic or myoclonic seizures • Catamenial epilepsy • Changes in seizure type with treatment • Early recurrence of seizures • Epileptic spasms • Focal to bilateral tonic-clonic seizures • Neonatal seizures • Photoparoxysmal response on EEG • Seizure triggers • Seizures in clusters
Epilepsy treatment	• Response to first ASM (7)	• ASM adverse effects • First ASM prescriber • Long latency between epilepsy onset and first ASM treatment • Number of ASMs in current regimen • Number of past ASM trials • Use of phenytoin or lamotrigine
Epilepsy etiology	• Cryptogenic epilepsy (7) • Hippocampal sclerosis (4) • Inborn error of metabolism (3) • Neuro-imaging abnormality (6) • Symptomatic epilepsy (12)	• Anoxic-ischemic encephalopathy • Cerebral neoplasm etiology • Chromosomic or monogenic disorder • Epileptic childhood syndrome (West syndrome, Lennox-Gastaut syndrome) • Epileptic encephalopathy • Infectious etiology

		• Malformation of cortical development (especially focal cortical dysplasia) • Progressive myoclonic epilepsy
Comorbidities	• Developmental delay (5) • Febrile seizures (4) • Neurological deficit (12) • Psychiatric comorbidity (in particular depression) (7)	• "Focal seizure-related comorbidities" including migraine, depression, anxiety, fractures, sprains and strains, open wounds, dislocation • Charlson comorbidity index • Dyslipidemia (diagnosis or treatment) • High ANA titer • High serum anti-GAD antibodies • Hypertension (diagnosis or treatment) • Poor academic perfomance • Retinal nerve fiber layer thinning
Genetic polymorphisms	• *ABCB1* gene (6)	• *ABCC2* gene • *APOE* gene • *CYP1*, *CYP2*, *CYP3* families of genes • *GABRA1*, *GABRA2*, *GABRA3* genes • *IL-1B-31 and IL-1RA* genes • *SCN2A* gene

ASM: antiseizure medication; ANA: antinuclear antibody; GAD: glutamic acid decarboxylase.

FIGURE LEGENDS

Figure 1. PRISMA flow diagram

Footnote: DRE= drug resistant epilepsy

Figure 2. Incidence of drug resistant epilepsy

Footnote: Studies reporting the incidence (95% confidence interval) of drug resistant epilepsy (DRE), stratified by (A) whether a population/community-based or clinic-based study, (B) whether the study used the International League Against Epilepsy (ILAE) definition of DRE or not (sorted by publication date), and (C) whether a study of children or adult/mixed ages.

Figure 3. Funnel plots for reporting bias

Footnote: Studies reporting (A) cumulative incidence for all studies and (B) prevalence for clinic-based studies.

Figure 4. Prevalence of drug resistant epilepsy, population/community-based versus clinic-based populations

Footnote: Studies reporting the prevalence (95% confidence interval) of drug resistant epilepsy (DRE), stratified by whether a population/community-based or clinic-based study.

Figure 5. Prevalence of drug resistant epilepsy, stratified various factors

Footnote: Studies reporting the prevalence (95% confidence interval) of drug resistant epilepsy, stratified by (A) whether the study used the International League Against Epilepsy (ILAE) definition of DRE or not (sorted by publication date), (B) whether a study of children or adult/mixed ages, (C) the epilepsy type, and (D) whether a study reporting point or period prevalence.

AUTHORS CONTRIBUTIONS

Author	Location	Contribution
Bushra Sultana	Montreal, Canada	Design of the study protocol, screening of the literature, data collection, drafting and critical revision of the manuscript.
Marie-Andrée Panzini	Montreal, Canada	Design of the study protocol, screening of the literature, data collection, critical revision of the manuscript.
Ariane Veilleux Carpentier	Montreal, Canada	Design of the study protocol, screening of the literature, data collection, critical revision of the manuscript.
Jacynthe Comtois	Montreal, Canada	Design of the study protocol, screening of the literature, data collection, critical revision of the manuscript.
Bastien Rioux	Montreal, Canada	Design of the study protocol, screening of the literature, data collection, critical revision of the manuscript.
Geneviève Gore	Montreal, Canada	Design of the study protocol, design of and execution of the search of electronic databases, critical revision of the manuscript.
Prisca R Bauer	Freiberg, Germany	Design of the study protocol, screening of the literature, data collection, critical revision of the manuscript.
Churl-Su Kwon	New York City, USA	Design of the study protocol, screening of the literature, data collection, critical revision of the manuscript.
Nathalie Jetté	New York City, USA	Design of the study protocol, screening of the literature, data collection, critical revision of the manuscript.
Colin B Josephson	Calgary, Canada	Design of the study protocol, screening of the literature, data collection, critical revision of the manuscript.
Mark R Keezer	Montreal, Canada	Design of the study protocol, screening of the literature, data collection, statistical analyses, drafting and critical revision of the manuscript.

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