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Review

Frequency of a false positive diagnosis of epilepsy: A systematic review of observational studies

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ABSTRACT

Purpose: To determine the frequency of false positive diagnoses of epilepsy and to explore its imitators and consequences.
Method: A systematic review of all published observational studies (to November 2015) was conducted to determine the proportion of false positive diagnoses of epilepsy. We included studies of people of all ages receiving a diagnosis of epilepsy. All observational study designs were included with the exception of case-reports and case series with fewer than 3 participants.
Results: Data were available from 27 studies (31 reports), reporting considerably varied frequencies of false positive diagnoses. The frequency of false positive diagnosis range from 2% to 71%. The data also suggest that syncope and psychogenic non-epileptic paroxysmal events were the commonest imitators of epilepsy. Misdiagnosis led to mismanagement with anti-epileptic drugs (AEDs) and affected legal driving status and employment.
Conclusions: False positive diagnosis of epilepsy is common, even though there is considerable heterogeneity across studies. All potential imitators should be considered and clinicians should be cautious introducing AEDs without a definite diagnosis given the risk of side effects, and the possible impact on legal driving status and employment.

1. Introduction

Newly diagnosed epilepsy is estimated at 47 per 100,000 person-years [1]. One study on 5000 people with epilepsy (PWE) from 15 European countries reported that 96% of PWE were prescribed antiepileptic drugs (AEDs), among whom 88% reported at least one side effect (e.g. tiredness, memory problems, difficulty in concentrating or thinking clearly, nervousness and agitation, etc.) and 31% had changed their AEDs at least once in the last year because of side effects [2]. In addition, a diagnosis of epilepsy can impact on many aspects of persons' life. It may affect the ability to get or maintain employment [3] and driving licence [4], impair health-related quality of life [5] and negatively impact on psychosocial functioning (e.g. experiencing stigma, anxiety and depression) [6,7]. Accordingly, misdiagnosis may result in people unnecessarily experiencing the adverse effects of AEDs, those psychological and social impacts and may contaminate research cohorts of people with epilepsy.

The diagnosis of epilepsy is challenging with a low correlation between referral and specialist diagnosis [8]. False positive diagnoses are thought to occur in up to 25% of patients [9,10]. Diagnosis is difficult due to varying seizure types and symptoms from visual hallucinations to tingling. Lack of awareness of imitators of epilepsy such as neuro-cardiogenic syncope [11], daydream and benign paroxysmal vertigo is a common cause of misdiagnosis [12]. To date, only non-systematic literature reviews [12–14] have explored this topic. We performed a systematic review to determine the frequency of false positive diagnoses of epilepsy and to explore its imitators and consequences.

2. Methods

The protocol of this review was registered in Prospero [15]. The published protocol was modified to exclude studies of epileptic seizure, as a result 4 studies reporting the false positive diagnosis

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of index epileptic seizure [16–19] were excluded. This review was restricted to published observational studies reporting the frequency of a false positive diagnosis of epilepsy. The study population included people (any age) who had been given an initial diagnosis of epilepsy. All observational study designs were included with the exception of case-reports and case series with fewer than 3 participants. All journal articles were included without language limitations. Studies were excluded if they had specific participant characteristic limits such as one sex (e.g. only males) or only people with disability with the exception of limits based on age.

2.1. Search strategy, data extraction and risk of bias assessment

Five databases were searched: MEDLINE, EMBASE, PsychINFO, CINAHL and AMED (from inception to 27 November 2015). The following search terms were used as free text or controlled vocabulary (i.e. medical subject headings, EMTREE) as appropriate for each database: epilepsy, seizures, convulsions, misdiagnosis, delayed diagnosis, diagnostic errors, incorrect diagnosis and missed diagnosis (full details available in the supplementary file). Titles and abstracts of all references were screened and full text articles were examined by three authors independently to determine whether they met the inclusion criteria. Further literature was sought through the reference lists of eligible studies. We did not check citation trails as early efforts indicated no yield.

Data extraction included region/country, recruitment site, study period, age, sample size, frequency of false positive diagnosis, aspects assessed to make the diagnosis and who made the diagnosis. Two researchers extracted data independently and cross-checked. When abstracts from conference were identified, we sought corresponding published journal articles. We reported data from the abstracts if corresponding journal articles could not be identified. We judged articles to be from the same cohort if there was evidence of overlapping recruitment sites, study dates, authorship and similar patient characteristics. Risk of bias was assessed using a 10-item assessment which reflected quality criteria for such studies.

3. Results

The search results and selection process are summarised in Fig. 1. A total of 2334 references were identified, of which 149 full text articles were retrieved to assess for inclusion/exclusion and a total of 27 studies (31 reports) were considered eligible. The frequency of misdiagnosis was calculated in only 7% of the study population in Ojeda 2012 [20]. We were unable to identify corresponding journal articles for five conference abstracts [20–24] (three studies) and one brief communication [25]. We included the abstract [24] but not the whole paper [26] from the one study, because the frequency of misdiagnosis was not reported in the latter.

3.1. Patient characteristics

Twenty-six studies (Table 1) (Ojeda 2012 not included) reported the frequency of false positive diagnosis on 6912 people with epilepsy. The largest study [11] contributed 22% of patients, with the remaining studies ranging in size from 17 [27] to 850 [28] patients. Four studies included paediatric patients (≤18 years) only [28–31]. Four were population-based [9,10,24,32] studies recruiting patients from a base population of 75,200 [32], 15,000 [24], 200,000 [9] and 40,000 [10], respectively. Five studies (nine reports [21–23,27,33–37]) recruited patients from head up tilt test (HUTT) or implantable electrocardiogram (ECG) recorder (ILR) centres. The remaining 17 studies recruited patients from epilepsy centres or tertiary hospitals. One study [25] recruited patients with pseudo-refractory epilepsy, five studies (seven reports [34–36,38–41]) recruited patients with refractory epilepsy.

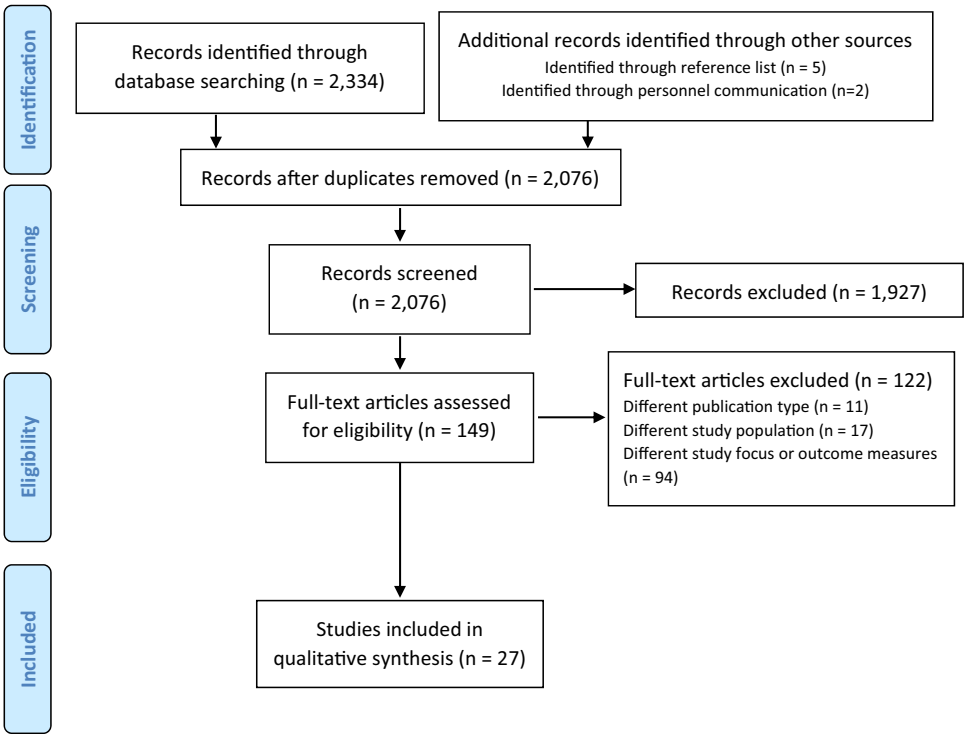

Fig. 1. PRISMA flow diagram for the systematic review process.

Table 1
Characteristics of studies on frequency of the false positive diagnosis of epilepsy.

First author year	Region/country	Recruitment site	Study period	Age (mean ± SD, range), years	Sample size/male (N)	False positive frequency (*n*), rate (%)	How was epilepsy diagnosed?	Who made the diagnosis?
Alsaadi 2004 [43]	California, USA	Inpatient epilepsy monitoring unit	Jul 2001–Dec 2002	–	113/–	22, 18.5%	Seizure description (initial) v-EEG with an automatic seizure detector (final)	An epileptologist or neurologist whose practice is greater than 50% epilepsy (initial)
Betts 1992 [46]	Birmingham, UK	Neuropsychiatry ward in a small psychiatric hospital	Jan 1983–Apr 1988	–	343/–	77–87, 22.4–25.4%	Clinical history, observation of the attacks, a-EEG, video-monitoring	Trained nursing staff, a neurophysiologist (final)
Edfors 2008 [33] §	Copenhagen, Denmark	Referred to HUTT from epilepsy specialist unit at University Hospital Righospitalet	Jan 2003–Mar 2005	40.6 ± 19.9, 15–88	120/78	85, 71%	–	GP, staff at different hospitals and epilepsy clinics and neurologists in private practice (initial)
Faulkner 2012 [47]	Sydney, Australia	Outpatient a-EEG at Royal Prince Alfred Hospital	2007–2010	–	210/–	67, 31.9%	Clinical record and EEG data (prolonged outpatient a-EEG) (final)	Two trained neurologists analysed EEG page by page independently (final)
Gibbs 1992 [28]	Liverpool, UK	Epilepsy clinic at Royal Liverpool Children's Hospital	Sep 1990–Aug 1991	1 mth – 16	850/–	81, 9%	EEG, neurological examination, CT (final)	GP, clinical (school) medical officer, hospital paediatric staff (initial) Staff at the clinic (final)
Hamid 2009 [21,22] Petkar 2009 [23] §	Salford, Greater Manchester, UK	A tertiary cardiology centre	1996–2006	50.9 ± 16.9, 19–80	62/25	8, 12.9%	ILR (final)	A neurologist or a GP (initial)
Hovorka 2007 [38] **	Prague, Czech Republic	v-EEG monitoring unit	2001–2003	–	249/–	56, 22.5%	v-EEG, seizure semiology, EEG, MRI, treatment with AED, potential psychiatric co-morbidities (final)	Study group (final)
Josephson 2007 [11] ¶	Halifax, Nova Scotia, Canada	Clinic	1988–2004	Adults (≥18)	1506/–	300, 19.9%	–	GP, general neurologists or ED physicians (initial) an adult neurologist whose predominant outpatient practice is epilepsy (final)
Karacan 2010 [31]	Erzurum, Turkey	Atatürk University Faculty of Medicine	Jul 2002–Jul 2009	9.35 1–18	119/74	3, 2.5%	EEG, echocardiography, HUTT, 24-h EEG treadmill tests if needed (final)	Paediatric cardiologist (final)
King 1982 [44]	Georgia, USA	Epilepsy unit at Medical College of Georgia	–	29.7 16–54	60/27	12, 20%	History, physical examination, laboratory and radiologic tests, v-EEG (final)	Two of the authors (final)
Kutlu 2013 [25] *	Ankara, Turkey	Department of Epilepsy in Ankara Research and Educational Hospital	Jun 2002–Dec 2011	29 ± 11.53 16–70	105/31	57, 54.3%	History, home video recording, EEG, MRI (final)	Staff in epilepsy department (final)
Labiner 2009 [24]	Arizona counties along the Arizona-Mexico border	–	–	–	171/–	15, 8.8%	–Δ	Two physicians (final)
LaRoche 2011 [27] §	Atlanta, Georgia, USA	HUTT and v-EEG centre at Emory University Hospital	Mar 2007–Dec 2008	–	17/–	8, 47.1%	HUTT, v-EEG (final)	–
Leach 2005 [9]	Wrexham, UK	26 general practices located within the Wrexham Maelor hospital catchment area	–	Inclusion criteria: 18–80	275/–	45, 16.3%	History of seizure disorder, investigations and nature of all treatments (final)	GP (initial) Experienced specialist registrar (final)
McCluggage 1984 [32]	Northern Ireland	7 general practices in Belfast, 1 in greater Belfast area and 1 rural practice, 35 miles from Belfast	1979–1981 18 month	–	247/–	5, 2%	Medical notes and a history from the patient or close relative (final) Δ	An independent epileptologist (final)
Miakotnykh 1990 [48]	Yekaterinburg (former Sverdlovsk), Russia (USSR)	Epilepsy clinic	–	–	635/–	70, 11%	EEG, echo encephalopathy, X-ray craniography, ophthalmoscopy and visual fields assessment (final)	Epileptologist (final)
Ojeda 2012 [20] &	Madrid, Spain	Epilepsy outpatient clinic	"2 year period"	–	22/–	4, 18.2%	Homemade video recordings (final) Δ	–

Table 1 (*Continued*)

First author year	Region/country	Recruitment site	Study period	Age (mean ± SD, range), years	Sample size/male (N)	False positive frequency (*n*), rate (%)	How was epilepsy diagnosed?	Who made the diagnosis?
Parra 1999 [45]	Chicago, Illinois, USA	4-bed inpatient video-EEG monitoring unit	"2 year period"	–	28/–	10, 35.7%	Combination of v-EEG, SPECT, MRI (final)	–
Rangel 2014 [35] 2012 [34] Freitas 2013 [36] § **	Porto, Portugal	Referrals to 'Autonomic Clinic for HUTT'	Jan 2000–Dec 2010	39 ± 17	94/27	31, 33%	Clinical (history and exam), negative HUTT, positive EEG consistent with epilepsy (final)	Neurologist (initial) Consensus between a neurologist and a cardiologist (final)
Scheepers 1998 [10] ¶	Cheshire, UK	David Lewis Centre in partnership with a group of general practices	Unknown	All ≥5 years	214/–	49, 22.9%	Clinical history including response to medication, seizure description, EEG and sometimes MRI and HUTT (final)	A consultant and an experienced epileptologist (final)
Smith 1999 [39] ¶,**	Liverpool, UK	A single consultant neurologist (referrals from various other doctors)	"12 months"	–	184/–	46, 26.1%	Clinical history based on individual account of their own symptoms and eyewitness account (final)	A single consultant neurologist (one of the authors) (final)
Smith 2002 [42]	Cardiff, UK	A monthly teenager clinic at Welsh Epilepsy Unit	46 months since Jan 1997	–	180/–	8, 4.4%	Medical history, physical examination, EEG (final) Δ	GP, paediatric neurologist, general paediatricians, physicians and psychiatrists (initial) An adult and a paediatric neurologist (final)
Stroink 2003 [29]	Netherlands	Referred by GP or paediatricians of the participating hospitals or in emergency	Since 1988 follow up for 2 years	5.4 inclusion criteria: 1 mth to 16	412/–	19, 4.6%	Postictal signs, possible provoking factors, medical history, family history, EEG, CT (final)	A panel of 3 paediatric neurologists with 10 years' experience in paediatric epilepsy (initial + final)
Uldall 2006 [30] ¶	Denmark	Dianalund Epilepsy Centre	"During 1997"	8.5 ?, 8 mths to 17 and 8 mths	223/120	87, 39%	Clinical, EEG, 62% v-EEG or a-EEG (final)	Two of the authors (final)
Viteva 2009 [40] *	Plovdiv, Bulgaria	Department of Neurology, Medical University	–	42.4 ± 13.4, 18–72	191/–	5, 2.6%	Medical documents, electrophysiological and neuroimaging (final) Δ	GP or neurologist (first) the research group (final)
Yogarajah 2008 [41] **	Buckinghamshire, UK	The Sir William Gowers Centre specialises in referrals for complex and severe cases of epilepsy	2004–2005	36	230/112	43, 18.7%	v-EEG, a-EEG, MRI, neuropsychological and neuropsychiatric evaluation, video cameras to record seizures witnessed on the unit (final) Δ	All professionals involved, including epileptologists, neuropsychiatrists, neuropsychologists and nursing staff (final)
Zaidi 2000 [37] §	Manchester, Chesbire and Salford, UK	Two outpatient epilepsy units: David Lewis Centre for Epilepsy and Hope Neurosciences Centre	–	38.9 ± 18, 16–77	74/33	31, 41.9%	HUTT and carotid sinus massage during continuous ECG, EEG, BP monitoring and long-term ILR (final)	

Abbreviations – v-EEG: video electroencephalography; a-EEG: ambulatory electroencephalography; ED: emergency department; NICU: neurological intensive care unit; GP: general practitioner; HUTT: head-up tilt testing; AED: anti-epileptic drug; ILR: implantable electrocardiogram (ECG) recorder; mth(s): month(s);

? This is median, not mean.

Δ International classification of epileptic seizures and international classification of epilepsy and epileptic syndromes defined by International League against Epilepsy was used in the final diagnosis.

¶ Studies reporting consequences of the false positive diagnosis of epilepsy.

§ Studies conducted at HUTT or ILR centres.

* Pseudo-refractory epilepsy.

** Refractory epilepsy.

Note: 36 out of the 74 study population in Zaidi 2000 were on adequate doses of anticonvulsant drugs (one drug in 21 patients, two drugs in 8 patients and three or more drugs in 7 patients) & Study excluded from the quantitative synthesis.

3.2. Diagnosis of epilepsy and frequency of false positive diagnosis

In six studies [20,24,32,40–42], the international classification of epileptic seizures and international classification of epilepsy and epileptic syndromes defined by International League against Epilepsy were used as the terminologies for the final diagnosis. Electroencephalogram (EEG) was used in 12 studies, video electroencephalography (v-EEG) was used in seven studies [27,30,38,41,43–45] and ambulatory electroencephalography (a-EEG) in four [30,41,46,47]. Staff with expertise in epilepsy made the final diagnosis in only seven studies [10,29,32,41,46–48]. The frequency of false positive diagnosis range from 2% to 71% (Fig. 2).

The proportions are presented stratified into subgroups on the basis of case selection (population-based, epilepsy centres or tertiary hospitals and Head up Tilt Test (HUTT), implantable electrocardiogram (ECG) recorder (ILR) centres). The squares are centred on the reported point estimates of effect; their size is large where the samples are larger, reflecting the relationship to the inverse of the variance. Horizontal lines represent 95% confidence intervals (CI).

3.3. Risk of bias assessment

In two studies (Table 2), the study population was not consecutively recruited, with one population-based study [9] excluding 357 patients already attending the local epilepsy clinic and one study [41] excluding 248 patients who underwent previous long-term EEG. In four studies, the diagnosis was not reassessed by staff with expertise in epilepsy, and in 15, it was unclear who made the final diagnosis or whether the person had been trained.

3.4. The differential diagnosis

1249 out of the 6912 patients in 26 studies (Ojeda 2012 not included) were given an incorrect diagnosis of epilepsy. For 906 patients in 18 studies the imitators of epilepsy were reported. We listed all the reported differential diagnoses and grouped them into eight categories (Fig. 3), according to a general epilepsy textbook [49]. Autism, mental retardation and learning disability were not mentioned in the textbook, but they were the predominant differential diagnoses in one study [30]. The "others" category included intoxication, encephalitis, massively reduced health condition, alcohol-related, post-anaesthetic, reaction to fright, hypoglycaemia and neoplasms. 475 cases of syncope from 15 studies and 314 cases of psychogenic non-epileptic paroxysmal events (NEPEs) from 12 studies were misdiagnosed as epilepsy.

3.5. The consequences of a false positive diagnosis

Four studies reported on the consequences of misdiagnosis [10,11,30,39]. More than one-third of people with a false positive

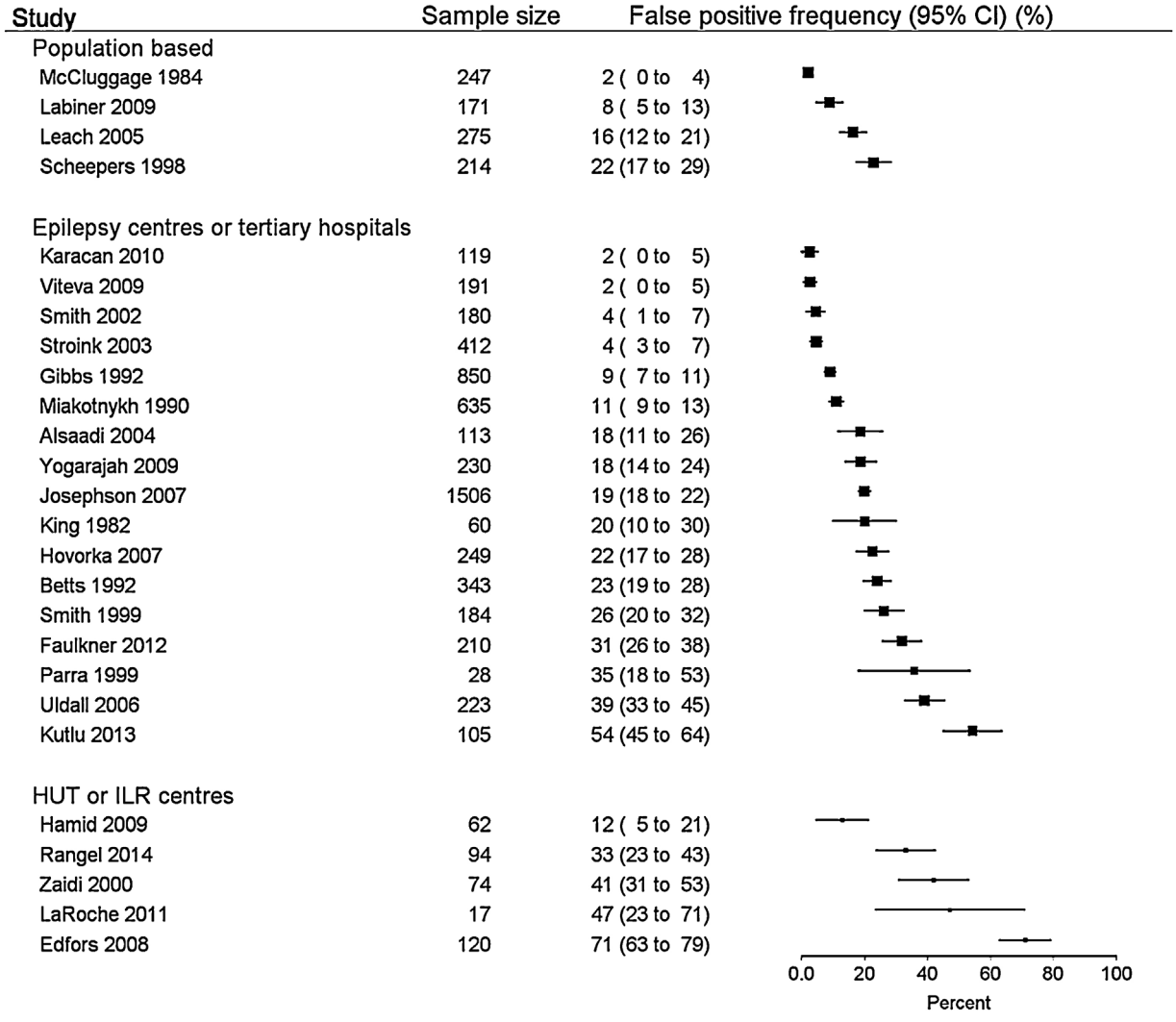

Fig. 2. Observational studies of the frequency of false positive diagnosis of epilepsy.

Table 2
Risk of bias assessment.

First author, year	1	2	3	4	5	6	7	8	9	10
Alsaadi 2004 [43]	✓	✓	×	✓	✓	✓	✓	✓	×	?
Betts 1992 [46]	✓	×	×	✓	✓	×	×	×	?	✓
Edfors 2008 [33]	✓	×	×	✓	×	×	✓	×	?	?
Faulkner 2012 [47]	✓	×	×	✓	✓	✓	✓	×	?	✓
Gibbs 1992 [28]	✓	✓	?	✓	✓	?	✓	✓	×	?
Hamid 2009 [21,22] Petkar 2009 [23]	×	✓	?	✓	×	×	✓	✓	✓	?
Hovorka 2007 [38]	✓	×	✓	✓	✓	×	✓	✓	✓	?
Josephson 2007 [11]	✓	×	×	✓	✓	✓	×	×	?	?
Karacan 2010 [31]	✓	✓	✓	✓	✓	×	✓	✓	✓	×
King 1982 [44]	✓	✓	✓	?	×	×	×	×	?	?
Kutlu 2013 [25]	×	×	×	✓	✓	✓	✓	×	?	?
Labiner 2009 [24]	×	✓	✓	✓	✓	✓	✓	×	?	?
LaRoche [27]	✓	×	×	✓	✓	×	×	×	?	?
Leach 2005 [9]	✓	✓	✓	×	✓	✓	✓	✓	✓	×
McCluggage 1984 [32]	✓	×	×	✓	✓	✓	✓	×	?	✓
Miakotnykh 1990 [48]	✓	✓	×	✓	✓	✓	✓	✓	✓	✓
Parra 1999 [45]	✓	×	✓	✓	×	×	×	×	?	?
Rangel 2012 [35] 2015 [34] Freitas 2013 [36]	✓	×	×	✓	✓	✓	✓	✓	✓	×
Scheepers 1998 [10]	✓	✓	✓	✓	✓	✓	✓	✓	×	✓
Smith 1999 [39]	✓	✓	×	✓	×	✓	✓	✓	×	×
Smith 2002 [42]	✓	✓	×	✓	×	✓	×	×	?	?
Stroink 2003 [29]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Uldall 2006 [30]	✓	✓	×	✓	×	✓	✓	✓	✓	?
Viteva 2009 [40]	✓	×	×	✓	✓	✓	×	×	?	?
Yogarajah 2008 [41]	✓	×	×	×	×	✓	✓	×	?	✓
Zaidi 2000 [37]	✓	✓	✓	✓	×	×	✓	✓	✓	?

✓ denotes yes; × no;? unable to determine.
1. Was this a journal article?
2. Was "the false positive diagnosis of epilepsy" the primary or secondary aim of the study?
3. Was data collection prospective?
4. Did the study population form a consecutive series?
5. Did all participants have "definite" diagnoses of epilepsy on referral? (If the diagnostic uncertainty was expressed on referral, the frequency was likely to be higher.)
6. Was the aetiology clear for all participants in the end? (In nine studies, the diagnosis of epilepsy was kept for some participants due to lack of occurrence of event during the study period and the frequency was likely to be lower.)
7. Were the denominator and numerator for the false positive frequency clearly reported?
8. Was the false positive frequency clearly reported?
9. Were the reported false positive frequency equal to what was calculated from the reported denominator and numerator?
10. Was the diagnosis re-judged by trained physicians in the field of epilepsy?

diagnosis of epilepsy were consequently mismanaged with AEDs. In one Canadian study, 67 (35%) out of 194 patients with neurocardiogenic syncope had been treated with AEDs, of whom adverse effects were reported in 35 (52%) [11]. Two cases of spontaneous abortion and one congenital left-sided hemiplegia were reported among the five pregnant women taking AEDs [11]. In one British study, 19 (39%) out of the 49 patients with misdiagnosis of epilepsy were on AEDs and 11 out of the 19 patients were on phenytoin and/or phenobarbital, without serum level monitoring [10]. In one Danish study, 35 (40%) out of the 87 children misdiagnosed with epilepsy were treated with AEDs [30].

Misdiagnosis also affected legal driving status and employment. Out of 194 patients with neurocardiogenic syncope in the Canadian study, driving licences were formally revoked for 27 patients and informally restricted for 38 patients, while job restrictions were placed on 11 (6%) patients as a result of transportation ($n = 8$) or health concerns ($n = 3$) [11]. In another British study, 12 out of the 14 who possessed a driving licence had driving interrupted; three patients lost full-time jobs, one was demoted and one had to refuse a job which involved driving [39].

4. Discussion

We report that the frequency of misdiagnosis of epilepsy range from 2% to 71%, with syncope and psychogenic NEPEs being the commonest imitators. Misdiagnosis leads to mismanagement with AEDs and affects legal driving status and employment. There was variation in estimates across studies due to potential moderator variables including the refractory/pseudo-refractory epilepsy, age of the study population, experience of the referring and consulting doctors, variations in the epilepsy diagnostic criteria used and methods to make the diagnosis (i.e. some or all of: written descriptions, videos of the episodes, EEG and neuroimaging), etc.

Lack of awareness of imitators is a common cause of misdiagnosis. Syncope is very common, with 15% of children and a similar percentage of middle aged men and women having "an episode" [50]. It is the sixth commonest cause of emergency admission in over 65-year olds in the UK [51]. HUTT and ILR have been suggested in patients with recurrent syncope and unexplained single syncope [50,52]. Despite the incidence of psychogenic NEPEs being 1.4 per 100,000 [53], 10–20% of patients referred to epilepsy centres have psychogenic NEPEs [54] Approximately 13% of patients with psychogenic NEPEs have coexistent epilepsy [55]. V-EEG is the gold standard for psychogenic NEPEs diagnosis [56]. Using data from v-EEG monitoring, researchers found that 50 of 52 patients with psychogenic NEPEs closed their eyes during the event, compared with 152 of 156 of patients with epilepsy, who kept their eyes open at the beginning of their event [57]. Without v-EEG, half of the psychogenic NEPEs were misclassified as epilepsy by neurologists based on history alone [58]. In addition, we acknowledge that a detailed history of events combined with EEG finding is the gold standard diagnostic method for epilepsy [49]. In this review, less than half of the studies used these methods. The value of clinical features and EEG has been highlighted. One study reported that an epileptic seizure is 5 times more likely than syncope if the patient is disoriented after the event and nausea or sweating are signs to exclude a seizure [59]. Another suggested when epilepsy is a reasonable possibility, a routine inter-ictal EEG can be a powerful diagnostic tool [60].

In the UK, the National Institute for Clinical Excellence guidelines state that only a specialist paediatrician with expertise in epilepsy should establish the diagnosis of epilepsy in children and young people [12], whereas specialist referral from general practitioners (GPs) is recommended after failure of two AEDs in Australia [61]. We are unable to compare the accuracy of diagnosis made by GPs, junior doctors or epileptologists, as most studies did not explicitly state who made the initial diagnosis. It was apparent that few studies involved epileptologists to determine the final diagnosis which may reflect suboptimal management of epilepsy patients.

Caution is suggested when prescribing AEDs, because when a presenting patient is taking AEDs, doctors' certainty about the diagnosis may be impacted and history taking may be influenced, in which suggestive terms, such as "warnings", "loss of consciousness", "tongue biting" will be used [62]. Conversely, delay in starting treatment does not affect long-term prognosis of first tonic–clonic seizure [63], early epilepsy or single seizures [64,65]. Nonetheless, we do not advocate delay if the diagnosis is clear as immediate AEDs treatment increases the time to second seizure and first tonic-clonic seizure, reduces the time to achieve 2-year remission of seizures [64], and leads to a significant reduction of the risk of relapse [66].

There are several limitations to this review. The considerable heterogeneity across studies makes a quantitative meta-analysis impossible. Second, the included studies were all conducted in developed countries, but developing countries have a higher median incidence rate of epilepsy (68.7/100,000) than developed

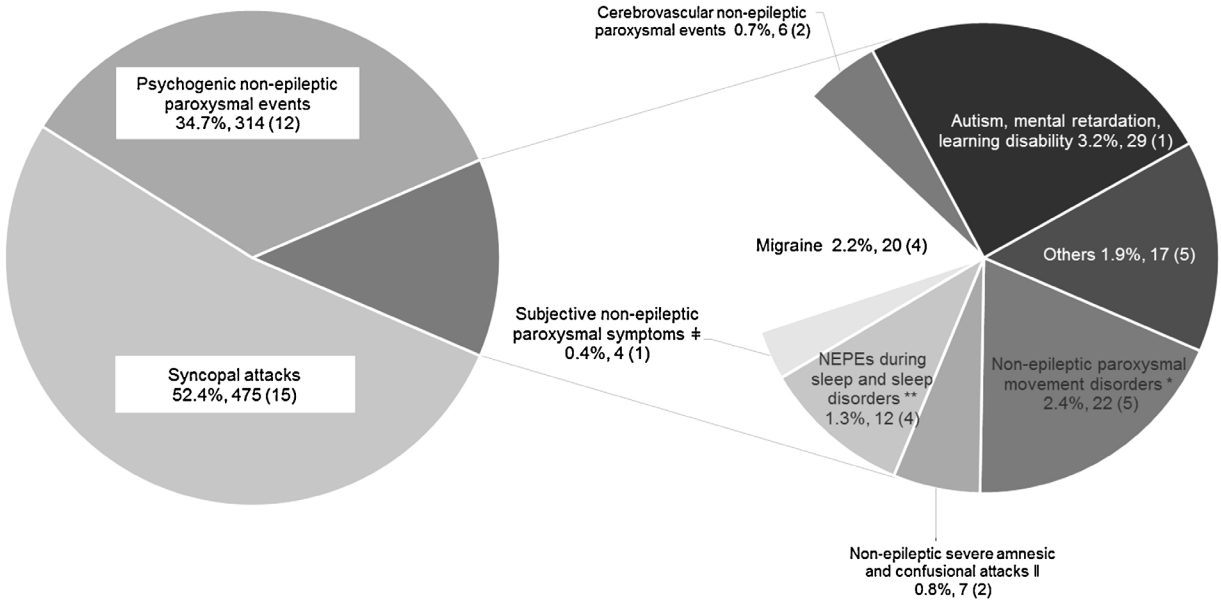

Fig. 3. Representation of the imitators of epilepsy in our study population. The percentages represent the proportions each category takes up. The figures outside the brackets are the number of cases. The figures inside the brackets are the number of studies reported such cases. * This included dystonia, myoclonus, familial paroxysmal kinesigenic choreoathetosis, tic disorders, tremor and hemiplegia. ? 7 cases were all daydreaming. ? 4 cases were all paroxysmal vertigo. ** This included parasomnia, sleep apnoea, narcolepsy, night terror and somnambulism.

countries (43.4/100,000) [1] and likely fewer resources for gold standard diagnosis. Finally, paroxysmal events in children with developmental delay, autism or learning difficulties are often misinterpreted as epilepsy [12], and they were the predominant differential diagnoses in one study [30] in this review. However, we are unable to provide a comprehensive overview of these groups as we excluded study populations limited by particular characteristics such as those with a disability.

In conclusion, misdiagnosis of epilepsy is common, even though there is considerable heterogeneity across studies. Potential imitators should be considered and clinicians should be cautious introducing AEDs without a definite diagnosis given the risk of side effects, and the possible impact on legal driving status and employment.

Conflict of interest statement

Dr. Anderson holds an NHMRC Senior Principal Research Fellowship. He receives personal fees and serves on the advisory board for Medtronic and Astra Zeneca. He receives travel reimbursement in 2016 from Takeda and Boehringer Ingelheim.

Dr. Hackett holds a National Heart Foundation Future Leader Fellowship, Level 2 (100,034, 2014–2017).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2016.08.005.

References

[1] Kotsopoulos IA, van Merode T, Kessels FG, de Krom MC, Knottnerus JA. Systematic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures. Epilepsia 2002;43:1402–9.
[2] Baker GA, Jacoby A, Buck D, Stalgis C, Monnet D. Quality of life of people with epilepsy: a European study. Epilepsia 1997;38:353–62.
[3] Lim KS, Wo SW, Wong MH, Tan CT. Impact of epilepsy on employment in Malaysia. Epilepsy Behav 2013;27:130–4.
[4] Vernon DD, Diller EM, Cook LJ, Reading JC, Suruda AJ, Dean JM. Evaluating the crash and citation rates of Utah drivers licensed with medical conditions, 1992–1996. Accid Anal Prev 2002;34:237–46.
[5] Modi AC, King AS, Monahan SR, Koumoutsos JE, Morita DA, Glauser TA. Even a single seizure negatively impacts pediatric health-related quality of life. Epilepsia 2009;50:2110–6.
[6] Quintas R, Raggi A, Giovannetti AM, Pagani M, Sabariego C, Cieza A, et al. Psychosocial difficulties in people with epilepsy: a systematic review of literature from 2005 until 2010. Epilepsy Behav 2012;25:60–7.
[7] Aydemir N, Kaya B, Yildiz G, Oztura I, Baklan B. Determinants of felt stigma in epilepsy. Epilepsy Behav 2016;58:76–80.
[8] Angus-Leppan H. Diagnosing epilepsy in neurology clinics: a prospective study. Seizure 2008;17:431–6.
[9] Leach J, Lauder R, Nicolson A, Smith D. Epilepsy in the UK: Misdiagnosis, mistreatment, and undertreatment? The Wrexham area epilepsy project. Seizure 2005;14:514–20.
[10] Scheepers B, Clough P, Pickles C. The misdiagnosis of epilepsy: findings of a population study. Seizure 1998;7:403–6.
[11] Josephson CB, Rahey S, Sadler RM. Neurocardiogenic syncope: frequency and consequences of its misdiagnosis as epilepsy. Can J Neurol Sci 2007;34:221–4.
[12] Chitre M. Pitfalls in the diagnosis and misdiagnosis of epilepsy. Paediatr Child Health (United Kingdom) 2013;23:237–42.
[13] Chowdhury FA, Nashef L, Elwes RD. Misdiagnosis in epilepsy: a review and recognition of diagnostic uncertainty. Eur J Neurol 2008;15:1034–42.
[14] van Donselaar CA, Stroink H, Arts W-F. How confident are we of the diagnosis of epilepsy? Epilepsia 2006;47(Suppl. 1):9–13.
[15] Xu Y, Nguyen D, Carcel C, Anderson C, Hackett M. Frequency of a false positive diagnosis of epilepsy or epileptic seizures: a protocol for a systematic review and meta-analysis of observational studies. In: PROSPERO: CRD42015030139; 2015. Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015030139.
[16] Boesebeck F, Freermann S, Kellinghaus C, Evers S. Misdiagnosis of epileptic and non-epileptic seizures in a neurological intensive care unit. Acta Neurol Scand 2010;122:189–95.
[17] Hamiwka LD, Singh N, Niosi J, Wirrell EC. Diagnostic inaccuracy in children referred with "first seizure": role for a first seizure clinic. Epilepsia 2007;48:1062–6.
[18] Moulin T, Sablot D, Vidry E, Belahsen F, Berger E, Lemounaud P, et al. Impact of emergency room neurologists on patient management and outcome. Eur Neurol 2003;50:207–14.

[19] Pinol-Ripoll G, Gomez Bitrian J, De La Puerta Gonzalez-Miro I, Royo Hernandez R, Mauri-Llerda JA. Characteristics and management of epileptic seizures in emergency department and diagnostic correlation at discharge. Anal Med Int 2008;25:168–72.
[20] Ojeda J, Ivanez V, Gutierrez-Gutierrez G, Lopez Gallardo S, Miralles A. Utility of homemade video recordings in epilepsy. Epilepsy Curr 2012;12.
[21] Hamid T, Rose S, Clifford A, Homa S, Garratt C, Clarke B, et al. 1 in 8 patients with syncope are misdiagnosed as epilepsy on long-term cardiac rhythm monitoring by an implantable ECG looprecorder (ILR). Epilepsia 2009;50:35.
[22] Hamid T, Rose S, Clifford A, Homa S, Garratt C, Clarke B, et al. Value of long term cardiac rhythm monitoring by an implantable ECG loop recorder (ILR) in patients presenting to the neurologist with transient loss of consciousness (T-LOC). J Neurol Sci 2009;285:S112.
[23] Petkar S, Hamid T, Rose S, Clifford A, Homa S, Garratt C, et al. 1 in 8 patients with syncope are misdiagnosed as epilepsy on long term cardiac rhythm monitoring by an implantable ECG loop recorder, Journal of Neurology. Neurosurg Psychiatry 2009;80.
[24] Labiner DM, Chong J. Under counting epilepsy: finding the undiagnosed along the Arizona-Mexico border. Epilepsia 2009;50:416–7.
[25] Kutlu G, Erdal A, Gomceli YB, Inan LE. Pseudo-refractory epilepsy. Neurosciences 2013;18:284–6.
[26] Chong J, Hesdorffer DC, Thurman DJ, Lopez D, Harris RB, Hauser WA, et al. The prevalence of epilepsy along the Arizona-Mexico border. Epilepsy Res 2013;105:206–15.
[27] LaRoche S, Taylor D, Walter P. Tilt table testing with video EEG monitoring in the evaluation of patients with unexplained loss of consciousness. Clin EEG Neurosci 2011;42:202–5.
[28] Gibbs J, Appleton RE. False diagnosis of epilepsy in children. Seizure: J Br Epilepsy Assoc 1992;1:15–8.
[29] Stroink H, Van Donselaar CA, Geerts AT, Peters ACB, Brouwer OF, Arts WFM. The accuracy of the diagnosis of paroxysmal events in children. Neurology 2003;60:979–82.
[30] Uldall P, Alving J, Hansen LK, Kibaek M, Buchholt J. The misdiagnosis of epilepsy in children admitted to a tertiary epilepsy centre with paroxysmal events. Arch Dis Child 2006;91:219–21.
[31] Karacan M, Bidev D, Olgun H, Tan H, Ceviz N. Cardiac or vasovagal syncope misdiagnosed as idiopathic epilepsy. Guncel Pediatr 2010;8:94–9.
[32] McCluggage JR, Ramsey HC, Irwin WG, Dowds MF. Anticonvulsant therapy in a general practice population in Northern Ireland. J R Coll Gen Pract 1984;34:24–31.
[33] Edfors R, Erdal J, A-Rogvi-Hansen B. Tilt table testing in patients with suspected epilepsy. Acta Neurol Scand 2008;117:354–8.
[34] Rangel I, Freitas J, Correia AS, Sousa A, Lebreiro A, De Sousa C, et al. The usefulness of the head-up tilt test in patients with suspected epilepsy. Seizure 2014;23:367–70.
[35] Rangel I, Freitas J, Sousa A, Correia AS, Lebreiro A, Paiva M, et al. Tilt table testing in patients with suspected epilepsy. Eur Heart J 2012;33:828.
[36] Freitas JP, Rangel I, Maciel MJ, Rocha-Goncalves F. Misdiagnosis epilepsy. Role of tilt table testing. Europace 2013;15:ii115.
[37] Zaidi A, Clough P, Cooper P, Scheepers B, Fitzpatrick AP. Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. J Am Coll Cardiol 2000;36:181–4.
[38] Hovorka J, Nežádal T, Herman E, Němcová I, Bajaček M. Psychogenic non-epileptic seizures, prospective clinical experience: diagnosis, clinical features, risk factors, psychiatric comorbidity, treatment outcome. Epileptic Disord 2007;9:S52–8.
[39] Smith D, Defalla BA, Chadwick DW. The misdiagnosis of epilepsy and the management of refractory epilepsy in a specialist clinic. QJM – Mon J Assoc Phys 1999;92:15–23.
[40] Viteva EI, Zahariev ZI. Pseudoresistance in patients with epilepsy – characteristics and determining factors. Folia Med (Plovdiv) 2009;51:33–9.
[41] Yogarajah M, Powell HW, Heaney D, Smith SJ, Duncan JS, Sisodiya SM. Long term monitoring in refractory epilepsy: the Gowers Unit experience. J Neurol Neurosurg Psychiatry 2009;80:305–10.
[42] Smith PE, Myson V, Gibbon F. A teenager epilepsy clinic: observational study. Eur J Neurol 2002;9:373–6.
[43] Alsaadi TM, Thieman C, Shatzel A, Farias S. Video-EEG telemetry can be a crucial tool for neurologists experienced in epilepsy when diagnosing seizure disorders. Seizure 2004;13:32–4.
[44] King DW, Gallagher BB, Murvin AJ, Smith DB, Marcus DJ, Hartlage LC, et al. 3rd pseudoseizures: diagnostic evaluation. Neurology 1982;32:18–23.
[45] Parra J, Iriarte J, Kanner AM. Are we overusing the diagnosis of psychogenic non-epileptic events? Seizure 1999;8:223–7.
[46] Betts T, Boden S. Diagnosis, management and prognosis of a group of 128 patients with non-epileptic attack disorder. Part I. Seizure 1992;1:19–26.
[47] Faulkner HJ, Arima H, Mohamed A. The utility of prolonged outpatient ambulatory EEG. Seizure 2012;21:491–5.
[48] Miakotnykh VS. Errors in the differential diagnosis of different types of nonepileptic paroxysms in the initial period of their occurrence. Zhurnal Nevropatologii i Psikhiatrii Imeni S – S – Korsakova 1990;90:13–8.
[49] Panayiotopoulos CP. A Clinical Guide to Epileptic Syndromes and their Treatment. 2nd ed. London: Springer; 2007.
[50] Brignole M, Alboni P, Benditt DG, Bergfeldt L, Blanc JJ, Bloch Thomsen PE, et al. Task Force on Syncope, E.S.o.C. Guidelines on management (diagnosis and treatment) of syncope – update 2004. Europace 2004;6:467–537.
[51] Kenny RA, O'Shea D, Walker HF. Impact of a dedicated syncope and falls facility for older adults on emergency beds. Age Ageing 2002;31:272–5.
[52] Brignole M, Menozzi C, Maggi R, Solano A, Donateo P, Bottoni N, et al. The usage and diagnostic yield of the implantable loop-recorder in detection of the mechanism of syncope and in guiding effective antiarrhythmic therapy in older people. Europace 2005;7:273–9.
[53] Sigurdardottir KR, Olafsson E. Incidence of psychogenic seizures in adults: a population-based study in Iceland. Epilepsia 1998;39:749–52.
[54] Benbadis SR, Allen Hauser W. An estimate of the prevalence of psychogenic non-epileptic seizures. Seizure 2000;9:280–1.
[55] Seneviratne U, Reutens D, D'Souza W. Stereotypy of psychogenic nonepileptic seizures: insights from video-EEG monitoring. Epilepsia 2010;51:1159–68.
[56] LaFrance Jr WC, Benbadis SR. Differentiating frontal lobe epilepsy from psychogenic nonepileptic seizures. Neurol Clin 2011;29:149.
[57] Chung SS, Gerber P, Kirlin KA. Ictal eye closure is a reliable indicator for psychogenic nonepileptic seizures. Neurology 2006;66:1730–1.
[58] Deacon C, Wiebe S, Blume WT, McLachlan RS, Young GB, Matijevic S. Seizure identification by clinical description in temporal lobe epilepsy: how accurate are we? Neurology 2003;61:1686–9.
[59] Hoefnagels WA, Padberg GW, Overweg J, van der Velde EA, Roos RA. Transient loss of consciousness: the value of the history for distinguishing seizure from syncope. J Neurol 1991;238:39–43.
[60] Goodin DS, Aminoff MJ. Does the interictal EEG have a role in the diagnosis of epilepsy? Lancet 1984;1:837–9.
[61] Tan M. Epilepsy in adults. Aust Fam Phys 2014;43:100–4.
[62] Oto M, Russell AJ, McGonigal A, Duncan R. Misdiagnosis of epilepsy in patients prescribed anticonvulsant drugs for other reasons. BMJ 2003;326:326–7.
[63] Leone MA, Solari A, Beghi E, Group F. Treatment of the first tonic–clonic seizure does not affect long-term remission of epilepsy. Neurology 2006;67:2227–9.
[64] Marson A, Jacoby A, Johnson A, Kim L, Gamble C, Chadwick D, et al. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. Lancet 2005;365:2007–13.
[65] Stroink H, Brouwer OF, Arts WF, Geerts AT, Peters AC, van Donselaar CA. The first unprovoked, untreated seizure in childhood: a hospital based study of the accuracy of the diagnosis, rate of recurrence, and long term outcome after recurrence. Dutch study of epilepsy in childhood. J Neurol Neurosurg Psychiatry 1998;64:595–600.
[66] Randomized clinical trial on the efficacy of antiepileptic drugs in reducing the risk of relapse after a first unprovoked tonic–clonic, seizure. First Seizure Trial Group (FIR.S.T. Group). Neurology 1993;43:478–83.