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Diagnostic criteria to aid the differential diagnosis of patients presenting with transient loss of consciousness: a systematic review

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Abstract

Background: Transient loss of consciousness (TLOC) is a common presentation in primary care. Over 90% of these are due to epilepsy, syncope, or psychogenic non-epileptic seizures (PNES). Misdiagnosis rates are as high as 30%.

Methods: Systematic review of inter-ictal clinical criteria to aid differential diagnosis of TLOC. We searched Medline, EMBASE, CINAHL and PsycInfo databases, as well as relevant grey literature depositories and citations of relevant reviews and guidelines for studies giving sensitivity and specificity of inter-ictal clinical characteristics used to differentiate between causes of TLOC. Two independent reviewers selected studies for inclusion and performed critical appraisal of included articles. We performed a narrative synthesis of included studies.

Results: Of 1023 results, 16 papers were included. Two compared syncope, epilepsy, and PNES; all others compared epilepsy and PNES. All were at significant risk of bias in at least one domain. 6 studied patient symptoms, 6 medical and social history, 3 witness reports and 1 examination findings. No individual criterion differentiated between diagnoses with high sensitivity and specificity.

Conclusions: There is a lack of validated diagnostic criteria to help clinicians assessing patients in primary or emergency care settings to discriminate between common causes of TLOC. Performance may be improved by combining sets of criteria in a clinical decision rule, but no such rule has been validated prospectively against gold-standard diagnostic criteria.

Highlights

- Systematically reviews inter-ictal criteria for differential of transient loss of consciousness
- Identifies lack of highly-predictive validated diagnostic criteria
- Identifies lack of decision rules validated against gold-standard reference diagnoses
- Future research should combine identified criteria in decision rules to support diagnosis

Keywords

Epilepsy; psychogenic non-epileptic seizures; syncope; differential diagnosis; systematic review

Introduction

Transient loss of consciousness (TLOC) – spontaneous disruption of consciousness with complete recovery not due to head trauma [1] – has a lifetime prevalence of 50%[2] and accounts for 3% of all emergency department (ED) attendances in the United Kingdom (UK).[3] Over 90% of presentations are due to epileptic seizures (ES), syncope, or psychogenic non-epileptic seizures (PNES).[4] Accurately distinguishing between these is vital to allow appropriate management and identification of patients at risk of morbidity/mortality from different underlying conditions.[3–5] Unfortunately, misdiagnosis rates for the causes of TLOC are high, with estimates ranging from 20-30%.[6–8] Diagnostic delay is particularly common in PNES, with a mean interval from initial manifestation to diagnosis of several years,[4] putting patients at high risk of iatrogenic injury and even death.[9] Most patients will not be assessed by a health professional during or in the immediate aftermath of a TLOC event, and the post-hoc diagnostic process is complicated by a lack of unique distinguishing clinical features;[3,4] the fact

that inter-episodal investigations are usually normal,[5] common investigations are low-yielding, [10] and any abnormalities detected often non-specific.[11]

The emergency or primary care management of many different presentations can be enhanced by clinical decision rules which have been shown to lead to more cost-effective care and improve patient outcomes.[12,13] However, there is no widely-accepted decision rule for differential diagnosis of TLOC.[2,14] Recent systematic reviews have explored the potential contribution of particular semiological features to the differential diagnosis [15–19], but the research studies underpinning these reviews were typically based on observations made during the video-EEG recording of episodes, not on more readily available but much less reliable information from witnesses [20,21]. Reviews of postictal serum biomarkers,[22,23] meanwhile, show that their utility is highly dependent on timely sampling and that they are not sufficiently reliable for diagnostic purposes in unselected patients in primary or emergency care settings. We seek to review the literature on candidate criteria for clinical decision rules for patients first presenting with TLOC, i.e. on features that may help guide the most appropriate further investigation and treatment of patients who were not assessed during or immediately after an episode.

Methods

We performed this systematic review according to a pre-specified (but not pre-registered) protocol, available from the authors on request. We perform the reporting below according to PRISMA guidelines.[24] It was based on primary research studies fulfilling the following eligibility criteria:

Eligibility criteria

Study type

- All research studies comparing the scope of clinical features or basic investigations, alone or in combination, to discriminate between at least two of E, S, and PNES.
- We excluded case reports/series, reviews, guidelines, or other synthesis or non-research articles.
- We excluded studies not in English.
- We imposed no limitation on publication date.

Participants

- Studies involving only patients ≥16 years old.
- Minimum sample size 5 patients per group.

- We excluded studies including participants with ES or PNES without disturbance of consciousness e.g. brief motor or purely sensory symptoms.

Reference test

- 'Gold-standard' diagnostic criteria.
    - E, PNES: Expert diagnosis using evidence from video-electro-encephalogram (vEEG) capture of an attack that is confirmed by patient and/or witnesses to be typical of the patient's usual attacks, with (E) or without (PNES) corresponding epileptiform EEG changes (corresponding to the highest ['documented'] level of certainty for the clinical diagnosis of PNES according to consensus criteria).[25]
    - S: Syncope expert diagnosis supported by pathophysiological evidence e.g. positive tilt-table test findings or syncopal/pre-syncopal symptoms synchronous with ECG or explanatory blood pressure changes.

Index tests

- Index tests should only involve information and investigations likely to be accessible for patients presenting to primary or emergency care settings post-episodally. If any index tests were identified that were not explicitly covered in the criteria below, two independent raters assessed their appropriateness for inclusion; in cases of disagreement a third rater settled the dispute.
- Included were:
    - Patient descriptions of attacks, peri-episodal and inter-episodal symptoms;
    - General medical history e.g. comorbidities;
    - Witness descriptions of attacks and collateral history;
    - Inter-episodal clinical examination;
    - Simple bedside investigations e.g. ECG.
- Excluded were:
    - Tests reliant upon direct observation of episodes;
    - Specialist investigations e.g. EEG, tilt-table testing;
    - Psychological inventories where results are not analysed at the individual-item level (as such inventories are impractical for use in the primary care clinical setting due both to time required and copyright issues);
    - Tests for which safety concerns may preclude performance in primary care e.g. induction procedures.
    - Laboratory blood tests (these were included in the initial protocol; however, authors subsequently agreed that, given the time-dependence of sampling their

use is limited in the contexts addressed by the review question. Other recent reviews address their utility in the diagnosis of TLOC in more immediate post-episodal settings).[22,23]

Outcomes

The primary outcome was diagnostic performance of index test compared to reference standard, quantitatively evaluated as sensitivity and specificity (or with sufficient data provided to allow calculation of these e.g. from contingency tables). For index tests comparing more than two populations, we required data sufficient to calculate overall diagnostic accuracy, accuracy for each diagnosis, and sensitivity/specificity for each diagnosis against all others.

Information sources and search strategy

We searched the Medline, EMBASE, CINAHL and PsycInfo databases to identify relevant papers, using strategies tailored to each database (Appendix 1) drawing on SIGN recommendations.[26] We also performed a free-text search of the OpenGrey grey literature repository, a hand -search of Cochrane database of systematic reviews for all studies under “Heart and Circulation”, “Neurology”, and “Mental Health” tagged as “diagnostic”. We also checked the reference sections of all identified studies, systematic reviews of related topics; and relevant NICE and ESC guidelines for additional relevant primary research studies.[2,27]

Study selection

A single reviewer (AW) screened the titles and abstracts of all initially identified to exclude papers clearly not relevant to the review question (e.g. incorrect article type, not addressing TLOC). Two reviewers (AW, EN) then independently performed more detailed screening of retained studies first by title and abstract, before evaluating full texts of all studies that had passed screening. Reviewers were not blinded to author or publication details. In cases of disagreement, we discussed between reviewers to reach consensus, with a third author (MR) available to adjudicate in cases of persistent dissensus.

Data collection and critical appraisal

Two reviewers (AW, EN) independently performed critical appraisal and data extraction, with disagreements resolved by discussion to reach consensus. We used a modified version of the QUADAS-2 tool for studies of diagnostic accuracy,[28] incorporating CASP checklist items,[29] to assess risk of bias. We extracted relevant data on a pre-specified data extraction form pilot-tested on three studies. Unless authors provided explicit theoretical or practical motivation for an alternative, we defined statistical significance at $\alpha = 0.05$; with studies involving multiple comparisons, we used the Bonferroni correction to maintain family-wise error rate (FWER) = 0.05; comparisons with uncorrected $p < 0.05$ were reported as trending toward significance.

Synthesis of results

Given the broad scope of the review question, we expected to find a range of different index criteria and a significant degree of clinical and methodological heterogeneity in our results; as such a quantitative, meta-analytic approach would be inappropriate. We instead performed a narrative and tabular synthesis of identified studies via content analysis, grouping them under pre-specified types: symptoms; history and comorbidities; witness reports; clinical examination; and simple investigations. We used the Cochrane Review Manager (RevMan) 5.3[30] to produce sensitivity and specificity forest plots for all results. The broad scope and likely heterogeneity of the index criteria limited the utility of quantitative/graphical assessment of publication bias, but we attempted to identify selective reporting during our synthesis. We appraised quality of evidence for each reported diagnostic criterion using GRADE criteria for diagnostic studies.[31,32]

Results

Study selection

Details of the study screening and evaluation process are highlighted in Fig. 1. Database searching was performed using the NICE Healthcare Databases Advanced Search (HDAS) tool, considering all articles published up to 13 December 2017. In addition to the initially captured studies, we also identified 13 relevant reviews that were included in citation searching.[15–19,22,23,27,33–37] One study was not evaluated as its full text was inaccessible and its authors did not respond to inquiries.[38] The most common reasons for exclusion were: diagnoses not confirmed by gold-standard investigations; combining study groups (several combined PNES and E; one combined PNES and S); mixed paediatric/adult populations; and insufficient information to evaluate performance of diagnostic criteria. Grey literature and hand-searching identified no further relevant studies. Citation searching identified a further two papers, as well as one potentially relevant paper that was inaccessible, whose authors did not respond to inquiries.[39]

Study characteristics

Table 1 summarises basic characteristics of included studies. Only two studies (using the same patient sample) included a syncope group;[4,40] all others compared ES with PNES. As some studies involved overlapping patient groups, we cannot state how many participants were captured by the studies overall. All studies were performed in industrialised OECD nations, the majority in the USA and the remainder in Western Europe. Half of included studies used a retrospective chart review to compare patient groups; others recruited participants prospectively. All participants were recruited from secondary/tertiary care settings, largely

from Epilepsy Monitoring Units (EMUs) (studies including a syncope patient group also recruited from individuals referred to a secondary-care syncope service[4,40]).

Critical appraisal

Table 2 summarises bias/applicability assessments. All included studies were at significant risk of bias in at least one domain. Most commonly, studies did not use separate patient groups for derivation and validation of an index test,[4,40–51] and/or did not pre-specify thresholds for that test.[4,40,42–44,46,47,49–51] Both of these are likely to result in model overfitting and significant over-estimation of performance. Frequently individuals involved in the index performance/evaluation were not blinded to results of the reference standard diagnosis [41–43,45,46,48–50] (and in some cases vice versa[41,45,46,48]), while several others provided insufficient information to appraise blinding (Table 1). Applicability concerns arose from the secondary care setting of all included studies. Box 1 summarises potential sources of bias

Box 1. Sources of bias in included studies

- Patient selection
  - No independent validation sample[4,40–45,45–51]
  - E or PNES not involving TLOC[43,51]
  - Case-control design[4,40,46]
  - Recruitment from specialist settings (potentially capturing a different patient group from those presenting with new-onset TLOC disorders).
  - Recruitment of patients with more chronic disorders
  - Recruitment of patients with disorders characterised by sufficiently frequent TLOC events for events to have been captured during monitoring of physiological functions
- Index test(s)
  - Test/threshold determined post-hoc[4,40,42–44,46,47,49–51]
  - Index test interpretation not blinded to reference[41–43,45,46,48–50]
  - Under-specification of index test[50]
  - Lack of certainty that other TLOC causes had been excluded in patients given a single “gold standard” diagnosis
- Reference standard
  - Reference standard interpretation not blinded to index test[41,45,46,48]
- Patient flow/timing
  - Large temporal interval between index and reference tests[49,50,52]

Results

Symptoms

We classified criteria utilising peri-episodal patient experiences[4,40,47,50] or aspects of a general review of symptoms (ROS)[43,46] as ‘symptom-based’ criteria. Two studies reported results from

the same patient sample; they were the only two studies to compare patients with all three common causes of TLOC (ES, syncope, and PNES)..[4,40] None featured independent validation samples.

Reuber et al.[4] found that an 86-item peri-episodal symptom questionnaire, together with basic demographic and historical details, predicted 78.4% of diagnoses accurately (syncope 91%, ES 66%, PNES 78%) via multinomial logistic regression. Most classification errors arose from labelling ES as PNES or vice versa. They did not provide results for individual symptoms, as the predictive models were based on a five-factor model onto which different symptom scores were weighted. In a post-hoc interpretation they described these as: 'feeling overpowered'; 'sensory experience'; 'amnesia'; 'mind/body/world disconnection'; and 'catastrophic experience'.

Rawlings et al. focused on panic symptoms in the same dataset, constructing an 'ictal panic score' from 7 panic-related symptoms in the questionnaire. They found that a receiver operating curve (ROC) statistic yielded an area under curve (AUC) of 0.74 for diagnosing PNES (against ES or S); a post-hoc threshold ictal panic score ≥ 12.5 identified PNES with a sensitivity of 71.1% and a specificity of 71.2%. They were less successful in discriminating ES from syncope, with AUCs for ES v (syncope or PNES) and syncope v (ES or PNES) of 0.44 and 0.32 respectively. These results are qualitatively consistent with Hendrickson et al's retrospective chart review of DSM-IV-TR panic symptoms present peri-episodally (AUC 0.782 for diagnosing PNES).

A recent systematic review suggests that observed ictal eye closure is less predictive of PNES than previously thought.[18] In their prospective study Syed et al. found that self-report does not differ significantly from chance (sensitivity=53.5%, specificity=50.7%). Ettinger et al. retrospectively examined post-ictal headache, lethargy, and confusion; while confusion did not differ significantly between ES and PNES ($p = 0.960$), both post-ictal headache ($p=0.008$, sensitivity=37.5%, specificity=95.7%) and lethargy did ($p=0.004$, sensitivity=56.3%, specificity=87.0%).

Two studies used ROS questionnaires to distinguish ES from PNES, hypothesising that PNES patients would endorse more complaints than those with E. The 79-item questionnaire used by Robles et al.[43] (AUC=0.845) performed better than the ten items proposed by Asadi-Pooya et al's[46] (AUC=0.67). Both studies derived post-hoc threshold percentages of positive complaints to diagnose PNES (Robles et al: sensitivity=78.3%. specificity=85.7% for ≥17% positive symptoms; Asadi-Pooya et al: sensitivity=40.0%, specificity=90.0% for >25% positive).

Fig. 2 summarises the findings of studies based on symptoms. As the vast majority of studies focused on ES and PNES populations, we present only sensitivity and specificity of criteria for the differentiation between ES and PNES. Given concerns regarding study design, indirectness of reported results as surrogates for patient-important outcomes, and non-representativeness of study samples, reported results constitute very low-quality evidence according to GRADE criteria.[31,32] This was also the case for all further outcomes reported below and as such we do not comment further on quality of evidence.

History

Historical criteria focus on aspects of the patient's background other than symptoms. Six studies used historical criteria, all involving ES and PNES groups: three focused on comorbidities;[41,45,48] one on trauma and psychiatric history;[51] two present combined history-based scores.[42,49] All except one[51] were retrospective notes reviews, and all were at high risk of bias in at least two domains. One conference presentation[49] provided very little information for critical appraisal; authors did not respond to requests for further data.

Comorbid conditions studied included chronic pain (CP),[41,42,45,49] fibromyalgia (FM),[41,42,45,49] chronic fatigue syndrome (CFS),[45] headache,[45,49] irritable bowel syndrome (IBS),[45] asthma,[45] gastro-oesophageal reflux disease (GORD),[45] mild traumatic brain injury (mTBI),[48] and psychiatric disorders including post-traumatic stress disorder (PTSD), depression, and panic or anxiety disorder, individually or in combination.[42,48,49,51]

Data at individual diagnosis level is available for some comorbidities. Benbadis et al. find that a diagnosis of CP or FM is highly specific (99%) for PNES, but with low sensitivity (9%);[41] Schramke et al., however, found no significant between-group difference.[42] Satpute et al. studied rates of mTBI prior to TLOC onset in US veterans, finding 50% sensitivity/75% specificity for PNES.[48] They also found between-group differences in rates of PTSD (clinical diagnosis by psychiatrist; sensitivity=63%/specificity=81.3%) and both PTSD and mTBI (sensitivity=41.3%/specificity=87.5%), though Arnold and Privitera found lower PTSD rates in a general EMU population (PTSD diagnosis [based on clinical assessment by a psychiatrist familiar with the structured questionnaire] yielding sensitivity=36% / specificity=85% for PNES).[51] Rates of depression and panic disorder (diagnosed by a psychiatrist as above) did not differ significantly between their ES and PNES groups, consistent with the findings of Schramke et al., who found depression, panic disorder, and anxiety disorder to be more prevalent in PNES, though only the latter (sensitivity=50%, specificity=78%) differentiated it significantly from ES ($p<0.002$, FWER = 0.05).[42] In the only prospective evaluation of comorbidity scores, Arnold and Privitera found no significant association between current or

lifetime Axis I or Axis II psychiatric diagnoses and PNES (uncorrected p>0.05).[51] Dixit et al.'s retrospective study used a pre-specified criterion of ≥1 diagnosis of a functional somatic syndrome (CFS, FM, CP, IBS) or chronic physical health condition with paroxysmal symptoms (headache, asthma, GORD) as an indicator of PNES (sensitivity=65.6% / specificity=73.0%).

Three studies evaluated historical criteria other than comorbidities. Arnold and Privitera found that a history of traumatic experience (especially sexual or physical abuse) predicted PNES (sensitivity=86%, specificity=67%).[51] Schramke et al. reviewed a range of historical criteria (determined by retrospective review of clinical interviews conducted by a psychologist at EMU admission).[42] They also found that childhood abuse or neglect significantly (p<0.002, FWER=0.05) predicted PNES (sensitivity=57%, specificity=88%). Other criteria significantly associated with PNES were marital instability, a family history of seizure disorder or alcohol abuse, and psychotropic medication use. Features that tended toward significance in predicting PNES (uncorrected p≤0.05) included a history of sexual abuse, female gender, a history of psychiatric hospitalisation or drug/alcohol abuse, a family history of CFS, fibromyalgia or psychiatric disorder, and an unstable work history. Features not predictive of a diagnosis included pending litigation or disability claims, a healthcare background, and a history of antisocial behaviour or head injury. Combining five highly-predictive features chosen for minimal covariance (age at first spell; psychiatric diagnosis other than depression or anxiety; marital instability; anxiety disorder; years of education) via logistic regression accounted for 44% of variance in classification outcome, with an accuracy of 87%.

The remaining study described a historical score incorporating age and social stressors at TLOC onset, comorbid psychiatric or chronic pain diagnoses, number of reported allergies, unusual seizure triggers, and a history of TLOC in healthcare setting or involving serious injury. The authors claimed 89.5% sensitivity and 88.5% specificity for PNES in the derivation sample using a score threshold derived post-hoc; no validation figures or AUC are given, indicating that these results are associated with a very high risk of bias.[49]

Fig.3 shows summary outcomes.

Witness reports

Three studies examined the contribution of witness reports, all focused on distinguishing ES from PNES. Syed et al.[20] used two independent epileptologists' evaluations of vEEG recordings to identify a set of three best semiological predictors of ES (eye-opening or widening at onset; abrupt onset; post-ictal confusion or sleep) and PNES (apparent preserved awareness; eye flutter; intensification/alleviation of attack by others), and then assessed whether witness-reports of these features predicted diagnosis in a validation sample. None of the reported features emerged as a statistically significant predictor in logistic regression. The

same group also found in an earlier study that witness report of another commonly-cited potentially diagnostic semiological feature of PNES, ictal eye closure, is a poor diagnostic criterion.[53]

These results contrast somewhat with the findings of Azar et al.,[44] who used a prospective blinded questionnaire design in a similar patient population to examine witness-reported semiology, both as single features and as a combined score derived post-hoc via logistic regression. Of twelve features described, they classified six as 'stronger' predictors (accuracy≥0.7): ictal eye opening, side-to-side head movements, and duration; and post-ictal deep, loud, or snoring breathing. Three were 'intermediate-strength' (0.7>accuracy≥0.6) – ictal mouth opening, and post-ictal irregular or prolonged abnormal breathing. The remaining three (continuous motor activity, limb synchrony, and post-ictal confusion) were poor predictors. In logistic regression, only ictal eye-opening and duration, and post-ictal deep, loud, or snoring breathing were statistically significant predictors. They claim that their post-hoc score could distinguish ES from PNES (sensitivity=84.2%, specificity=84.6%) but provide insufficient information to support this statement.

Fig. 4 shows summary outcomes.

Examination

A single study considered postictal examination findings to differentiate between TLOC causes.[52] Oliva et al retrospectively reviewed the presence of intra-oral lacerations on examination of EMU patients, finding the presence of oral lacerations (tongue, cheek, or lip) was specific (100%) but not sensitive (26%) for ES (see fig 5).

Relevant excluded papers

The review process highlighted several studies that did not meet the original inclusion criteria but which the authors feel worthy of comment in that they go further than any of the included studies in developing and validating CDRs for differential diagnosis of TLOC at first presentation, and additionally include syncope patient groups.

We identified two candidate CDRs for discriminating between syncope and 'seizures' at first presentation in primary or emergency care. The most comprehensively evaluated of these is the 9-point witness/symptom score developed by Sheldon et al,[54] which predicts syncope versus seizures or on the basis of six criteria positively correlated with seizures (waking with cut tongue, witness-reported abnormal behaviour [amnesia, unresponsiveness, unusual posturing or limb jerking], association with emotional stress, post-ictal confusion, unilateral head-turning, and prodromal deja/jamais vu), and three correlated with syncope (presyncope, loss of consciousness with prolonged standing or sitting, and pre-episodal diaphoresis). The

original study quoted sensitivity and specificity of 94% for seizures in a separate validation sample of patients; independent prospective validation claims sensitivity and specificity for syncope of 86.54% and 92.13%.[55] However, these studies do not distinguish ES from PNES, and did not use gold-standard vEEG-based diagnostic criteria for defining the seizure group; Sheldon et al state that the 'seizure' group contained patients with generalised seizures and focal with secondary generalisation, determined by 'positive' EEG alone. A briefer, four-point score proposed by Hoefnagels et al predicted ES versus syncope "or other causes" on the basis of: post-episode disorientation; lack of pre-episodal diaphoresis; age ≤ 45y; and tongue-biting. They report only that expected frequencies "agree well" with observed frequencies and did not validate their model on a separate sample. Furthermore, diagnosis of ES was based purely on semiological criteria (clonic movement, automatism, or aura) and no clear criteria for diagnosis of syncope were given, limiting applicability of their results.

Two further studies provided CDRs for distinguishing ES from PNES. Kerr et al. propose an 11-point history-based score (using information on comorbidities, gender, and medication history) to distinguish ES (all forms except temporal-lobe epilepsy) and PNES in a combined paediatric and adult patient group. They found that a history of migraines, asthma, and chronic pain, as well as overall number of comorbidities predicted PNES, while diabetes mellitus and non-metastatic neoplasia suggested E; female gender and overall number of non-anti-epileptic or psychiatric medications were also predictive of PNES, while the number of current and previously tried antiepileptic drugs predicted E. Their regression-based score identified PNES with 90% sensitivity and 55% specificity in a validation sample.[56] Syed et al. adopted a different approach from conventional regression-based CDR development, developing a classifier to predict PNES using machine-learning methods able to exploit non-linear interactions between predictors.[57] Their classifier predicted PNES on the basis of 53 patient-reported questionnaire responses covering a range of psychosocial variables with 85% sensitivity and specificity, though patients with comorbid ES were also present in the PNES group and no syncope group was included.

Discussion

This review highlights that there is a lack of validated diagnostic criteria to help clinicians assessing patients in primary or emergency care settings to discriminate between the common causes of TLOC; ES, syncope and PNES. All included studies focused on patients in secondary/tertiary-care settings, who may differ from patients at first presentation in important respects. Only two studies aiming to identify potential diagnostic criteria included patients with S, [4,40] although the most pressing concern in the initial diagnostic assessment by a non-expert clinician may be the differentiation between syncope on the one hand and seizures (ES or

PNES) on the other. Many patients with syncope may be adequately managed in emergency or primary care settings. Only some will require further investigation (typically by experts in cardiology or internal medicine). The most appropriate management of patients presenting with TLOC in the context of a new seizure disorder (E or PNES) is likely to require referral to a clinician with expertise in the diagnosis and treatment of such disorders (typically a neurologist).

Candidate diagnostic criteria were generally limited by poor sensitivity or specificity. Prediction rates were improved by combining individual features in a number of studies, [49,54,56,58,59] but none of these combination scores have so far been validated prospectively against gold-standard diagnoses in settings in which unselected patients present and many of the proposed scores do not discriminate between all common causes of TLOC.

The review protocol introduced two important sources of potential bias. The requirement of a gold-standard diagnosis as reference standard necessarily excludes participants for whom such a diagnosis is not reached. Exclusion of these 'difficult to diagnose' patients overestimates performance of index tests.[28] Furthermore, the requirement that patients had gold-standard diagnoses meant that in all included studies participants were recruited from secondary/tertiary care settings, leading to significant applicability concerns. Patients referred to specialist services (EMUs, syncope services) are likely to differ from those with a first presentation of TLOC in duration of symptoms, complexity of symptoms, difficulty of diagnosis, and other dimensions. Settings may also differ in the relative frequency of different diagnoses (for instance, PNES may be over-represented and epilepsy underrepresented in EMU compared to primary care settings). This is notable as the diagnostic value of particular observations will in part depend on the frequency distribution of the different diagnoses in the population studied. Furthermore, by requiring pathophysiological evidence to support expert diagnosis in our 'gold-standard' criterion for syncope diagnosis, we would potentially exclude patients for whom a clear diagnosis of vasovagal syncope could, according to current guidelines, be made on the basis of history alone.[60] However, on reviewing excluded studies none was excluded for this reason alone.

It is also important to note that all included studies were conducted in industrialised OECD nations in the Western hemisphere. It is feasible that some of the factors identified would not have the same diagnostic potential in less-industrialised or non-Western nations (for instance, gender distribution of PNES and association with sexual abuse may differ between USA/Western Europe and Iran[61] or China[62]).

This review demonstrates the need for development and validation of diagnostic tools to aid differential diagnosis of TLOC. Machine-learning classifiers have the potential to exploit non-

linear interactions between predictors,[57] although they may be challenging to implement in primary care. A predictive tool would not need to classify patients perfectly; even if imperfect, it could be used to guide initial investigation and referral pathways. Furthermore, such a quantitative measure could provide a numeric pre-test probability of particular diagnoses that would help with the interpretation of test results.[63] Ideally a diagnostic tool used in this setting would also identify TLOC presentations of patients at particular risk – for instance of sudden cardiac death or Sudden Unexpected Death in Epilepsy (SUDEP).

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Tables

STUDY	SETTING	COUNTRY	DESIGN	INDEX TEST(S)	PATIENT GROUPS (*n*)	MEAN (SD) AGE (y)	GENDER (F:M)	BLINDING TO GROUP	FUNDING
Symptoms									
Robles *et al* 2015[43]	Patients referred to EMU	USA	Retrospective chart review	Proportion of positive answers on ROS questionnaire	ES (23)	43.2 (14.1)	13:10	No blinding of index to reference	NS
					PNES (21)	38.8 (11.8)	15:6		
Rawlings *et al* 2017[40 d]	Postal recruitment of patients referred to EMU or syncope service	UK	Prospective; exploratory	"Ictal panic score" from 9 panic symptoms	ES (95)	31[a] (15)[b]	68:27	NS	Hospital charity; local research body; NIHR (UK)
					PNES (98)	43[a] (22)[b]	69:29		
					S (100)	57.5[a] (44)[b]	77:23		
Asadi-Pooya *et al* 2016[46]	Patients referred to EMU	USA	Retrospective chart review	Proportion of positive answers on 10-question ROS questionnaire	ES (30)	29.5 (8.3)	21:9	No blinding of index to reference or vice versa	No specific funding
					PNES (30)	27.7 (6.9)	21:9		
Reuber *et al* 2016[64 d]	Postal recruitment of patients referred to EMU or	UK	Prospective questionnaire	Peri-episodal symptom questionnaire – prediction via factor analysis	ES (100)	35.4 (14.5)	71:29	NS	Hospital charity
					PNES (100)	41.6 (13.5)	71:29		

	syncope service			dimensional reduction and logistic regression	S (100)	53.5 (21.6)	77:23		
Hendrickson *et al* 2014[47] [e]	Patients referred to EMU	USA	Retrospective chart review	Number of DSM-IV-TR panic symptoms present peri-episodally	ES (130)	NS	61:69	NS	NS
					PNES (224)	NS	167:57		
Ettinger *et al* 1999[50]	Patients referred to EMU	USA	Retrospective chart review	Post-episodal headache, fatigue, lethargy or confusion	ES (16)	39	11:5	NS	NS
					PNES (23)	43	19:4		
History									
Benbadis 2005[41]	Patients referred to EMU	USA	Retrospective chart review	Documented diagnosis of CP or FM	ES (734)	NS	NS	No blinding of index to reference or vice versa	NS
					PNES (308)				
Schramke *et al* 2010[42]	Patients referred to EMU	USA	Retrospective chart review	Logistic regression based on historical criteria	ES (93)	35.9 (12.1)	60:33	No blinding of index to reference	NS
					PNES (61)	40.2 (16.7)	47:14		
Dixit *et al* 2013[45] [e]	Patients referred to EMU	USA	Retrospective chart review	≥1 comorbid diagnosis of: CFS; FM; CP; headache; IBS; asthma; GORD	ES (122)	NS	57:65	NS	NS
					PNES (158)	NS	118:40		
		USA			ES (16)	NS	NS	Not blinded	NS

Satpute *et al* 2014[48]	VA patients referred to EMU		Retrospective chart review	Comorbid diagnoses of PTSD or mTBI prior to onset	PNES (46)	NS	NS		
Bozorg *et al* 2009[49]	Patients referred to EMU	USA	Retrospective chart review	8-item history-based score	ES, PNES; *N* = 45 overall	NS	NS	Not blinded	NS
Arnold & Privitera 1996[51]	Patients referred to EMU	USA	Prospective; exploratory	History of psychiatric diagnosis or trauma; combined via logistic regression	ES (27)	35	13:14	Index blinded to reference	NS
					PNES (14)	33	9:5		
Witness reports									
Azar *et al* 2010[44]	Patients referred to EMU	USA	Prospective cohort	12-point structured witness questionnaire	SE (19)	18-62[c]	33:12	Witnesses blinded to diagnosis	NS
					PNES (26)				
Syed *et al* 2008[53]	Patients referred to EMU	USA	Prospective cohort	Witness and patient self-reports of ictal eye closure	ES (69)	38.2 (12.9)	43:26	NS	NS
					PNES (43)	41.5 (13.0)	34:9		
Syed *et al* 2011[20]	Patients referred to EMU	USA	Prospective cohort	48-point structured witness questionnaire	ES (23)	36[a] (19-65)[c]	NS	NS	NS
					PNES (12)	39[a] (19-55)[c]	NS		
Examination									
Oliva *et al* 2008[52]	Patients referred to EMU	USA	Retrospective chart review	Presence of oral laceration	ES (66)	37.4 (1.7)	31:35	Unclear	NS
					PNES (18)	40.4 (2.7)	11:7		

Table 1. Characteristics of included studies.
A = Absence seizures. BDNF = Brain-derived neurotrophic factor. CFS = chronic fatigue syndrome. CK = creatine kinase. CP = chronic pain. ES = Epileptic Seizures. EMU = Epilepsy Monitoring Unit. FM = fibromyalgia. FS = focal seizure with secondary generalisation. GORD = gastro-oesophageal reflux disease. GTC = Generalised tonic-clonic seizure. HC = healthy controls. IBS = irritable bowel syndrome. mTBI = Mild traumatic brain injury. NS = Not stated. NSE = neuron-specific enolase. PNES = psychogenic non-epileptic seizures. PRL = prolactin. PTSD = Post-traumatic stress disorder. ROS = review of symptoms. S = syncope. *VA = US Veterans' Administration.*
[a]Median value
[b]IQR
[c]Range
[d,e]Denote studies involving same or overlapping participants
[f]Analysis performed at individual episode level; participant demographics not given

	Risk of bias				Concerns regarding applicability			
	PATIENT SELECTION	INDEX TEST(S)	REFERENCE STANDARD	PATIENT FLOW + TIMING	PATIENT SELECTION	INDEX TEST(S)	REFERENCE STANDARD	PATIENT FLOW + TIMING
Symptoms								
Robles *et al* 2015[43]	High	High	High	Unc	Y	N	N	N
Rawlings *et al* 2017[40]	High	High	Low	High	Y	N	N	N
Asadi-Pooya *et al* 2016[46]	High	High	High	Unc	Y	N	N	N
Reuber *et al* 2016[64]	High	High	Low	High	Y	N	N	N
Hendrickson *et al* 2014[47]	High	High	Unc	Unc	Y	N	N	N
Ettinger *et al* 1999[50]	High	High	High	Low	Y	N	N	N
History								
Benbadis 2005[41]	High	High	High	Unc	Y	N	N	N
Schramke *et al* 2010[42]	High	High	Low	Low	Y	N	N	N
Dixit *et al* 2013[45]	High	High	High	Unc	Y	N	N	N
Satpute *et al* 2014[48]	High	High	High	Unc	Y	N	N	N
Bozorg *et al* 2009[49]	High	High	Low	High	Y	N	N	N
Arnold & Privitera 1996[51]	High	High	Low	Low	Y	N	N	N
Witness reports								
Azar *et al* 2010[44]	High	High	Unc	Low	Y	N	N	N
Syed *et al* 2008[53]	Low	Low	Unc	Low	Y	N	N	N
Syed *et al* 2011[20]	Low	High	Unc	Low	Y	N	N	N
Examination								
Oliva *et al* 2008[52]	Low	Low	Unc	Low	Y	N	N	N

Table 2. Summary of critical appraisal and assessment of applicability of included studies. Y = Yes. N = No. Unc = Unclear.

Figures

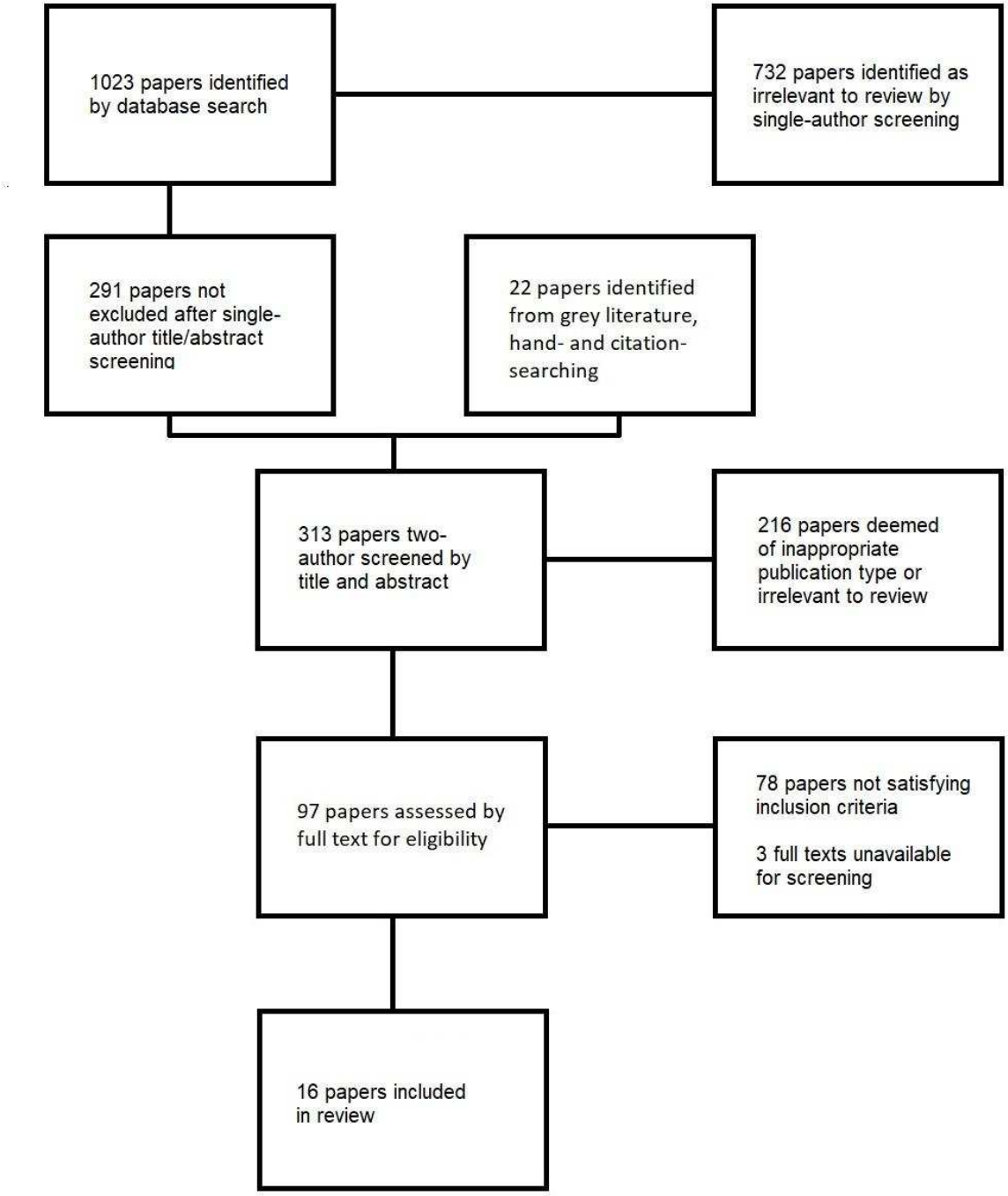

Figure 1. Flow of studies identified in literature search

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
ROS questionnaire								
Asadi-Pooya et al 2016	12	3	18	27	0.40 [0.23, 0.59]	0.90 [0.73, 0.98]		
Robles et al 2015	16	3	5	20	0.76 [0.53, 0.92]	0.87 [0.66, 0.97]		
Ictal panic								
Hendrickson et al 2014	185	45	39	85	0.83 [0.77, 0.87]	0.65 [0.57, 0.74]		
Rawlings et al 2017[a]	70	56	28	139	0.71 [0.61, 0.80]	0.71 [0.64, 0.78]		
Ictal eye closure								
Syed et al 2008	23	34	20	35	0.53 [0.38, 0.69]	0.51 [0.38, 0.63]		
Absence of post-ictal headache								
Ettinger et al 1999	22	10	1	6	0.96 [0.78, 1.00]	0.38 [0.15, 0.65]		
Absence of post-ictal lethargy								
Ettinger et al 1999	20	7	3	9	0.87 [0.66, 0.97]	0.56 [0.30, 0.80]		
Absence of post-ictal confusion								
Ettinger et al 1999	18	10	5	6	0.78 [0.56, 0.93]	0.38 [0.15, 0.65]		
Peri-episodal symptoms questionnaire								
Reuber et al 2016[b]	76	25	19	71	0.80 [0.71, 0.88]	0.74 [0.64, 0.82]		

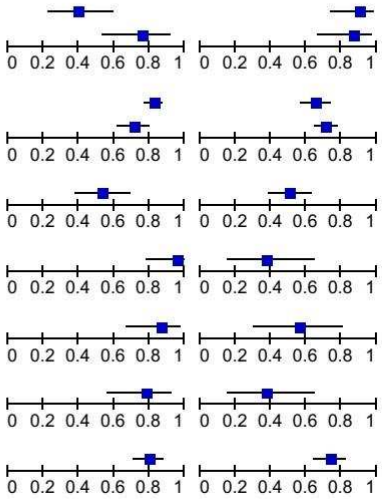

Figure 2. Summary outcomes for symptom-based criteria for detecting PNES
[a]Quoted figure compares PNES group v (E or S)
[b]Sensitivity and specificity for pairwise logistic regression comparing PNES v E

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Chronic pain or fibromyalgia								
Benbadis 2005	27	9	281	725	0.09 [0.06, 0.12]	0.99 [0.98, 0.99]		
Schramke et al 2010	1	0	60	93	0.02 [0.00, 0.09]	1.00 [0.96, 1.00]		
PTSD								
Arnold + Privitera 1996	5	4	9	23	0.36 [0.13, 0.65]	0.85 [0.66, 0.96]		
Satpute et al 2014	29	3	17	13	0.63 [0.48, 0.77]	0.81 [0.54, 0.96]		
mTBI								
Satpute et al 2014	23	4	23	12	0.50 [0.35, 0.65]	0.75 [0.48, 0.93]		
Depression								
Arnold + Privitera 1996	5	7	9	20	0.36 [0.13, 0.65]	0.74 [0.54, 0.89]		
Schramke et al 2010	31	25	30	68	0.51 [0.38, 0.64]	0.73 [0.63, 0.82]		
Anxiety disorder								
Schramke et al 2010	31	20	30	73	0.51 [0.38, 0.64]	0.78 [0.69, 0.86]		
Panic disorder								
Arnold + Privitera 1996	3	3	11	24	0.21 [0.05, 0.51]	0.89 [0.71, 0.98]		
Schramke et al 2010	15	8	46	85	0.25 [0.14, 0.37]	0.91 [0.84, 0.96]		
Axis I psychiatric diagnosis								
Arnold + Privitera 1996	10	14	4	13	0.71 [0.42, 0.92]	0.48 [0.29, 0.68]		
Axis II psychiatric diagnosis								
Arnold + Privitera 1996	5	5	9	22	0.36 [0.13, 0.65]	0.81 [0.62, 0.94]		
Comorbid functional somatic or chronic paroxysmal condition								
Dixit et al 2013	104	33	54	89	0.66 [0.58, 0.73]	0.73 [0.64, 0.81]		
Traumatic experience								
Arnold + Privitera 1996	12	9	2	18	0.86 [0.57, 0.98]	0.67 [0.46, 0.83]		
Childhood abuse or neglect								
Schramke et al 2010	26	17	35	76	0.43 [0.30, 0.56]	0.82 [0.72, 0.89]		
Marital instability								
Schramke et al 2010	43	42	18	51	0.70 [0.57, 0.81]	0.55 [0.44, 0.65]		
Family history of seizure disorder								
Schramke et al 2010	19	14	42	79	0.31 [0.20, 0.44]	0.85 [0.76, 0.92]		
Family history of alcohol abuse								
Schramke et al 2010	30	21	31	72	0.49 [0.36, 0.62]	0.77 [0.68, 0.85]		
Psychotropic medication use								
Schramke et al 2010	32	21	29	72	0.52 [0.39, 0.65]	0.77 [0.68, 0.85]		

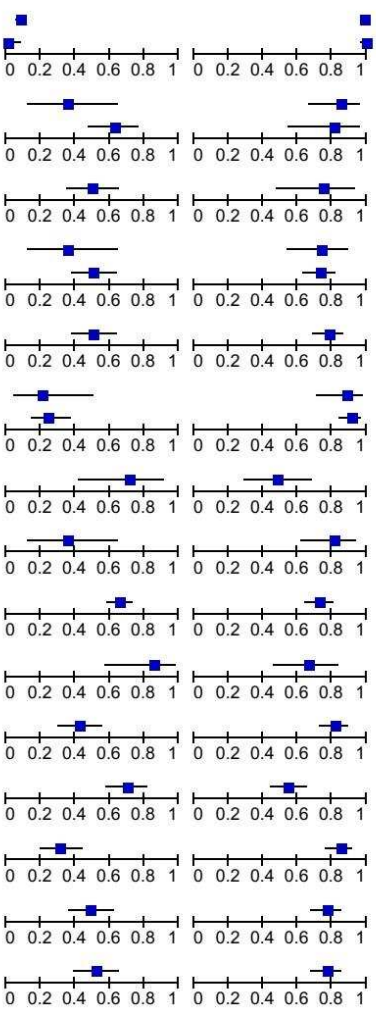

Figure 3. Summary outcomes for historical criteria for detecting PNES

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ictal eye closure						
Azar et al 2010	20	4	6	12	0.77 [0.56, 0.91]	0.75 [0.48, 0.93]
Syed et al 2008	18	36	25	33	0.42 [0.27, 0.58]	0.48 [0.36, 0.60]
Syed et al 2011	3	4	9	19	0.25 [0.05, 0.57]	0.83 [0.61, 0.95]
Ictal mouth closure						
Azar et al 2010	18	4	8	6	0.69 [0.48, 0.86]	0.60 [0.26, 0.88]
Discontinuous motor activity						
Azar et al 2010	11	18	13	0	0.46 [0.26, 0.67]	0.00 [0.00, 0.19]
Syed et al 2011	6	10	6	13	0.50 [0.21, 0.79]	0.57 [0.34, 0.77]
Side-side head movements						
Azar et al 2010	15	4	8	15	0.65 [0.43, 0.84]	0.79 [0.54, 0.94]
Syed et al 2011	2	6	10	17	0.17 [0.02, 0.48]	0.74 [0.52, 0.90]
Dissynchrony of limb movements						
Azar et al 2010	14	15	10	0	0.58 [0.37, 0.78]	0.00 [0.00, 0.22]
Syed et al 2011	7	8	5	15	0.58 [0.28, 0.85]	0.65 [0.43, 0.84]
Episode duration >2 minutes						
Azar et al 2010	21	4	5	12	0.81 [0.61, 0.93]	0.75 [0.48, 0.93]
Syed et al 2011	7	18	5	5	0.58 [0.28, 0.85]	0.22 [0.07, 0.44]
Post-ictal shallow breathing						
Azar et al 2010	17	6	4	13	0.81 [0.58, 0.95]	0.68 [0.43, 0.87]
Syed et al 2011	3	4	9	19	0.25 [0.05, 0.57]	0.83 [0.61, 0.95]
Post-ictal quiet breathing						
Azar et al 2010	23	5	3	11	0.88 [0.70, 0.98]	0.69 [0.41, 0.89]
Absence of post-ictal snoring						
Azar et al 2010	22	6	4	10	0.85 [0.65, 0.96]	0.63 [0.35, 0.85]
Syed et al 2011	10	19	2	4	0.83 [0.52, 0.98]	0.17 [0.05, 0.39]
Post-ictal irregular breathing						
Azar et al 2010	16	7	7	12	0.70 [0.47, 0.87]	0.63 [0.38, 0.84]
Duration of post-ictal abnormal breathing <1 minute						
Azar et al 2010	17	7	4	5	0.81 [0.58, 0.95]	0.42 [0.15, 0.72]
Absence of post-ictal confusion						
Azar et al 2010	25	19	0	0	1.00 [0.86, 1.00]	0.00 [0.00, 0.18]
Syed et al 2011	0	5	12	18	0.00 [0.00, 0.26]	0.78 [0.56, 0.93]
Non-abrupt episode onset						
Syed et al 2011	3	12	9	11	0.25 [0.05, 0.57]	0.48 [0.27, 0.69]
Preserved ictal awareness						
Syed et al 2011	3	4	9	19	0.25 [0.05, 0.57]	0.83 [0.61, 0.95]
Ictal eye flutter						
Syed et al 2011	5	11	7	12	0.42 [0.15, 0.72]	0.52 [0.31, 0.73]
Intensification or alleviation of attack by others						
Syed et al 2011	3	4	9	19	0.25 [0.05, 0.57]	0.83 [0.61, 0.95]

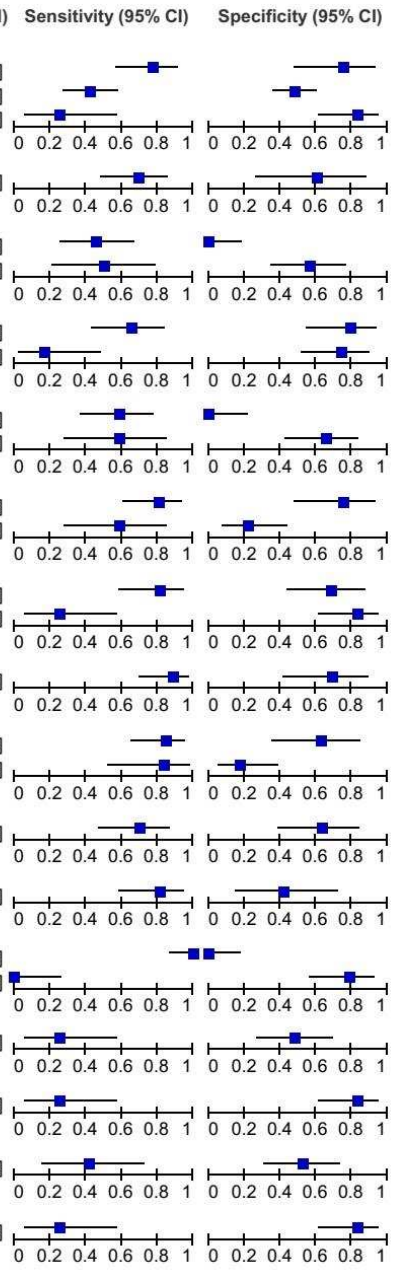

Figure 4. Summary outcomes for witness reports for detecting PNES

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Absence of oral lacerations						
Oliva et al 2008	18	49	0	17	1.00 [0.81, 1.00]	0.26 [0.16, 0.38]

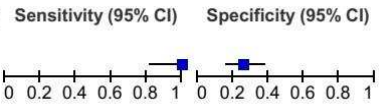

Figure 5. Summary outcomes for examination criteria for detecting PNES

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Appendix 1: Search strategy

Search strategy for identifying diagnostic studies developed from that suggested by SIGN.[26]

Filter for excluding irrelevant article types from NICE.[65]

MEDLINE, CINAHL

Condition filter

1. (pseudoseizure* OR pseudo-seizure* OR non-epileptic* OR nonepileptic* OR (psychogenic ADJ3 seizure) OR (psychogenic ADJ3 convulsion) OR (psychogenic ADJ3 event) OR (psychogenic ADJ3 episode) OR (psychogenic ADJ3 attack) OR (hyster* ADJ3 seizure) OR (hyster* ADJ3 convulsion) OR (hyster* ADJ3 event) OR (hyster* ADJ3 episode) OR (hyster* ADJ3 attack) OR hysteroepilepsy OR dissoc*).ti,ab
2. Exp EPILEPSY/di
3. Exp SEIZURES/di
4. (epilep*).ti,ab.
5. (seizure*).ti,ab.
6. exp SYNCOPE/di
7. (syncop* OR faint*).ti,ab.
8. OR/2-5
9. 6 OR 7
10. 1 AND 8
11. 1 AND 9
12. 8 AND 9
13. OR/10-12
14. (black?out* OR collapse OR T?LOC OR ((brief OR transient OR temporary OR paroxysmal OR short) ADJ3 ((los* ADJ2 conscious*) OR unconscious*))).ti,ab
15. 13 OR 14

Diagnostic study filter

16. exp SENSITIVITY AND SPECIFICITY/ (not CINAHL)
17. sensitivity.ti,ab.
18. specificity.ti,ab.
19. ((pretest OR pre-test) adj probability).ti,ab.
20. (predictive ADJ value*).ti,ab.
21. (likelihood ADJ ratio*).ti,ab.
22. (post-test ADJ probability).ti,ab.
23. (decision ADJ rule*).ti,ab.
24. (diagnos* ADJ2 scor*).ti,ab.
25. (diagnos* ADJ2 criteri*).ti,ab.
26. OR/16-25

Article type exclusion filter

27. (letter).pt
28. (editorial).pt
29. (historical article).pt
30. (anecdote).pt
31. (commentary).pt

32. (note).pt
33. (case report*).pt
34. (case study).pt
35. OR/27-34

Final search

36. 15 AND 26
37. 36 NOT 35

EMBASE

Condition filter

1. (pseudoseizure* OR pseudo-seizure* OR non-epileptic* OR nonepileptic* OR (psychogenic ADJ3 seizure) OR (psychogenic ADJ3 convulsion) OR (psychogenic ADJ3 event) OR (psychogenic ADJ3 episode) OR (psychogenic ADJ3 attack) OR (hyster* ADJ3 seizure) OR (hyster* ADJ3 convulsion) OR (hyster* ADJ3 event) OR (hyster* ADJ3 episode) OR (hyster* ADJ3 attack) OR hysteroepilepsy OR dissoc*).ti,ab
2. Exp EPILEPSY/di
3. Exp SEIZURE/di
4. (epilep*).ti,ab.
5. (seizure*).ti,ab.
6. exp FAINTNESS/di
7. (syncop* OR faint*).ti,ab.
8. OR/2-5
9. 6 OR 7
10. 1 AND 8
11. 1 AND 9
12. 8 AND 9
13. OR/10-12
14. (black?out* OR T?LOC OR ((brief OR transient OR temporary OR paroxysmal OR short) ADJ3 ((los* ADJ2 conscious*) OR unconscious*))).ti,ab
15. 13 OR 14

Diagnostic study filter

16. exp SENSITIVITY AND SPECIFICITY/
17. exp DIAGNOSTIC ACCURACY/
18. exp DIAGNOSTIC VALUE/
19. exp PREDICTIVE VALUE/
20. sensitivity.ti,ab.
21. specificity.ti,ab.
22. ((pretest OR pre-test) adj probability).ti,ab.
23. (predictive ADJ value*).ti,ab.
24. (likelihood ADJ ratio*).ti,ab.
25. (post-test ADJ probability).ti,ab.
26. (decision ADJ rule*).ti,ab.
27. (diagnos* ADJ2 scor*).ti,ab.
28. (diagnos* ADJ2 criteri*).ti,ab.
29. OR/16-28

Article type exclusion filter

30. (letter).pt

31. (editorial).pt
32. (historical article).pt
33. (anecdote).pt
34. (commentary).pt
35. (note).pt
36. (case report*).pt
37. (case study).pt
38. OR/30-37

Final search

39. 15 AND 29
40. 39 NOT 38

PsycInfo

Condition filter

1. (pseudoseizure* OR pseudo-seizure* OR non-epileptic* OR nonepileptic* OR (psychogenic ADJ3 seizure) OR (psychogenic ADJ3 convulsion) OR (psychogenic ADJ3 event) OR (psychogenic ADJ3 episode) OR (psychogenic ADJ3 attack) OR (hyster* ADJ3 seizure) OR (hyster* ADJ3 convulsion) OR (hyster* ADJ3 event) OR (hyster* ADJ3 episode) OR (hyster* ADJ3 attack) OR hysteroepilepsy OR dissoc*).ti,ab
2. Exp EPILEPSY/di
3. Exp SEIZURES/di
4. (epilep*).ti,ab.
5. (seizure*).ti,ab.
6. exp SYNCOPE/di
7. (syncop* OR faint*).ti,ab.
8. OR/2-5
9. 6 OR 7
10. 1 AND 8
11. 1 AND 9
12. 8 AND 9
13. OR/10-12
14. (black?out* OR collapse OR T?LOC OR ((brief OR transient OR temporary OR paroxysmal OR short) ADJ3 ((los* ADJ2 conscious*) OR unconscious*))).ti,ab
15. 13 OR 14

Diagnostic study filter

16. sensitivity.ti,ab.
17. specificity.ti,ab.
18. ((pretest OR pre-test) adj probability).ti,ab.
19. (predictive ADJ value*).ti,ab.
20. (likelihood ADJ ratio*).ti,ab.
21. (post-test ADJ probability).ti,ab.
22. (decision ADJ rule*).ti,ab.
23. (diagnos* ADJ2 scor*).ti,ab.
24. (diagnos* ADJ2 criteri*).ti,ab.
25. OR/16-24

Final search

15 AND 25 [Record type Authored Book OR Book OR Chapter OR Dissertation OR Dissertation Abstract OR Edited Book OR Journal OR Journal Article OR Peer-reviewed Journal OR Reference Book]