

Review

Dual diagnosis of epilepsy and psychogenic nonepileptic seizures: Systematic review and meta-analysis of frequency, correlates, and outcomes[☆]

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ARTICLE INFO

Article history:

Received 6 September 2018

Revised 6 October 2018

Accepted 7 October 2018

Available online 29 October 2018

Keywords:

Epilepsy

Psychogenic nonepileptic seizure

Comorbidity

Dual diagnosis

Dissociative seizure

Psychogenic

ABSTRACT

Comorbid epilepsy and psychogenic nonepileptic seizures (PNES) represent a serious challenge for the clinicians. However, the frequency, associations, and outcomes of dual diagnosis of epilepsy and PNES are unclear.

The aim of the review was to determine the frequency, correlates, and outcomes of a dual diagnosis. A systematic review of all published observational studies (from inception to Dec. 2016) was conducted to determine the frequency, correlates, and outcomes of dual diagnosis. We included studies of individuals of any age reporting a dual diagnosis of epilepsy and PNES. All observational study designs were included with the exception of case reports and case series with fewer than 10 participants.

The mean frequency of epilepsy in patients with PNES across all studies was 22% (95% confidence intervals [CI] 20 to 25%, range: 0% to 90%) while the mean frequency of PNES in patients with epilepsy was 12% (95% CI 10 to 14%, range: 1% to 62%). High heterogeneity means that these pooled estimates should be viewed with caution. A number of correlates of dual diagnosis were reported. Some studies delineated differences in semiology of seizures in patients with dual diagnosis vs. PNES or epilepsy only. However, most of the correlates were inconclusive. Only a few studies examined outcome in patients with dual diagnosis.

Dual diagnosis is common in clinical practice, especially among patients referred to specialized services, and requires careful diagnosis and management.

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1. Introduction

Psychogenic nonepileptic seizures (PNES) are genuinely experienced events resembling epilepsy but without the concomitant electrophysiological electrical activity [1]. The clinical presentation of PNES and epilepsy can be similar. However, approaches to their management are radically different. Epilepsy requires anticonvulsant therapy, in certain cases, surgery and other nonpharmacological methods, while modern etiological models of PNES find that it has much in common with panic disorder and can benefit in a similar way from explanation and psychotherapeutic interventions [2].

In some cases, PNES and epilepsy coexist. According to different estimates, between 8% and 60% of patients with PNES also have epilepsy [3]. A number of factors could contribute to the development of PNES in epilepsy such as psychiatric comorbidities, cognitive dysfunction, the experience of unpredictable seizures, and problems with social adaptation [4].

To our knowledge, there is no systematic review exploring the frequency, associations, and outcomes of comorbid epilepsy in patients with PNES and vice versa. These data are important for early identification of those who are at risk of the development of comorbid epilepsy and PNES and planning treatment. The aim of the review was to determine the frequency, correlates, and outcomes of dual diagnosis of epilepsy and PNES.

2. Methods

The systematic review was undertaken following Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines [5] for

[☆] Author contributions: MK searched reference lists, extracted the data, and wrote first draft. YX searched databases and performed statistical analysis. All authors take part in the planning of the paper, critically reviewed, revised, and approved the final draft.

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meta-analysis of observational studies and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6].

2.1. Search strategy and data extraction

Five databases were searched: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica dataBASE (EMBASE), Psychological Information Database (PsycINFO), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Allied and Alternative Medicine (AMED) (from inception to 11 Dec. 2016). The following search terms were used as free text or controlled vocabulary (i.e., medical subject headings, Emtree) as appropriate for each database: 'epilepsy' AND 'seizure', 'attack', 'non-epileptic', 'psychogenic', 'dissociative', 'conversion', 'functional' (full details available in the supplementary file). Titles and abstracts of all references were screened by one author (YX), and full text articles were examined by another (MK) to determine whether they met the inclusion criteria. Further literature was sought through the reference lists of eligible studies (MK). Data extraction included region/country, recruitment site, study period, age, sample size, frequency of dual diagnosis, method of diagnosis, and who made the diagnosis. One researcher (MK) extracted data. When abstracts from conferences were identified, we sought corresponding published journal articles. We reported data from the abstracts only 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. We included all published observational studies reporting the frequency of people with dual diagnosis of epilepsy and PNES or associations of comorbid epilepsy and PNES as a primary or secondary outcome regardless of duration of the disease. All observational

study designs were accepted with the exception of case report and case series of fewer than 10 participants.

All studies were divided into high- and low-quality groups. The studies were qualified as low-quality if they had either specific participant characteristic limits such as one sex, disabled, but not age or convenience, selective, or random sampling. Risk of bias was assessed using a 10-item assessment, which reflected quality criteria for such studies [7].

2.1.1. Statistical analysis

Studies' reported frequency of comorbid epilepsy and PNES was pooled. We conducted quantitative synthesis and produced forest plots in Stata 13 using random effects analysis. Subgroup analysis was conducted based on the recruitment site (i.e., specialized centers, neuropsychiatry units, psychiatry departments, neuropsychology units, hospitals, population-based, databases) and study population (i.e., adults, adults in epilepsy surgery series, children, adults, veterans, intractable seizures, elderly). Statistical heterogeneity and consistency were assessed using the standard Q statistic, with $p < 0.05$ and I^2 .

3. Results

The search results and selection processes are summarized in Fig. 1. A total of 2773 references were identified, of which 175 full text articles were retrieved to assess for inclusion/exclusion, and a total of 117 studies (122 reports) were considered eligible. Included papers contained data obtained from 17,478 people. Two studies were population-based [8,9] while the rest were hospital-based [1,3,4,10–126]. In the latter, patients were recruited mostly from highly specialized epilepsy centers (tertiary hospitals, academic departments, comprehensive epilepsy programs – 112 of 118 studies). Sixty-nine studies were retrospective, and 49 were prospective. Children were recruited in seven studies,

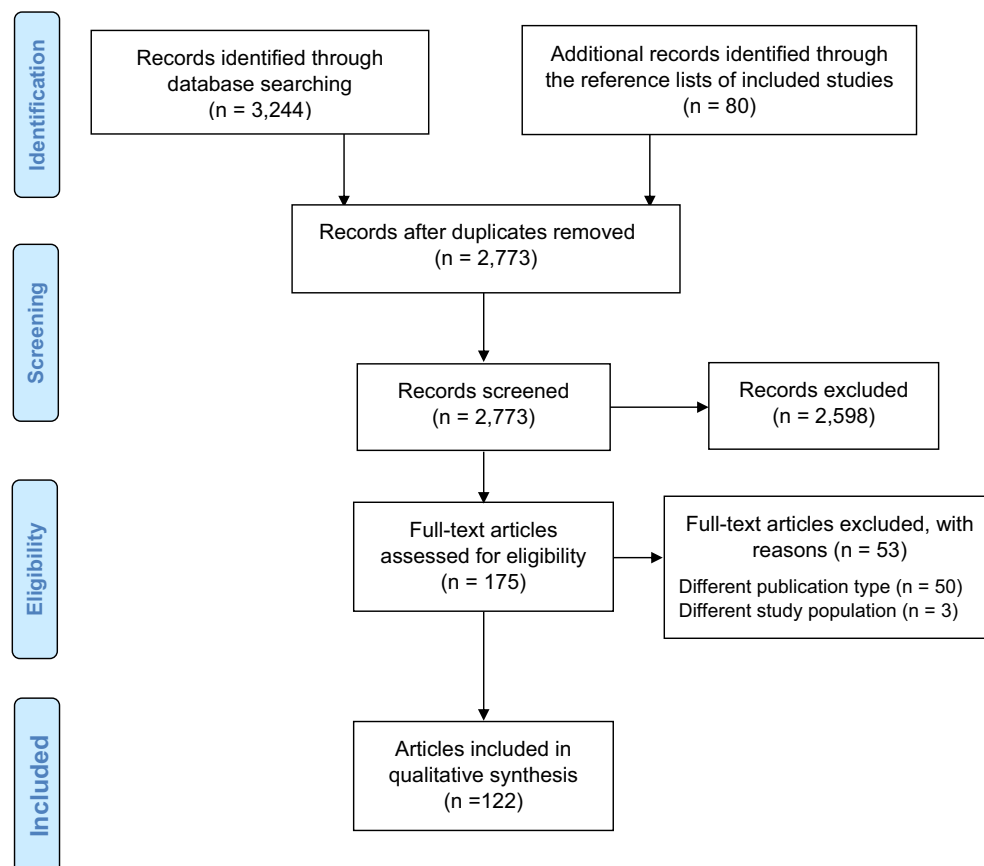


Fig. 1. PRISMA flow diagram for the systematic review process.

three of which specifically included those with intractable seizures. In one study, patients with juvenile myoclonic epilepsy of different ages were included. One hundred and nine studies were restricted to adults, of which some were exclusively of specific subpopulations: elderly or veterans ($n = 7$), surgical series ($n = 6$), treatment-resistant epilepsy ($n = 5$), "mental retardation" ($n = 1$), and traumatic brain injury ($n = 1$). In 72 studies, patients with dual diagnosis were compared with those with PNES. In 21 studies, patients with dual diagnosis were compared with those with PNES and with epilepsy. The method of diagnosis of epilepsy/PNES was video-electroencephalography monitoring (VEM) in 102 of 118 studies.

3.1. Frequency of dual diagnosis

The frequency of epilepsy in patients with PNES varied from 0% to 90% while the frequency of PNES in patients with epilepsy varied from 1% to 62%.

The pooled frequency of epilepsy among those with PNES was 22% (95% confidence interval [CI] 20 to 25%) (Fig. 2). The pooled frequency of PNES among those with epilepsy was 12% (95% CI 10 to 14%) (Fig. 3). In both cases, the level of heterogeneity (I^2) of included studies was high i.e., 96.5 and 92.7% correspondingly, $p = 0.0001$.

Meta-analysis of the data according to the site of recruitment yielded similar results. The pooled frequency of dual diagnosis varied from 2% (95% CI 1 to 4%) among those recruited from epilepsy surgery programs (3 studies, $n = 2872$) up to 42% (95% CI 11 to 72%) among patients from (neuro)psychiatric departments and neuropsychology units (3 studies, $n = 161$). In the two population-based studies, the pooled frequency of epilepsy among those with PNES (2 studies, $n = 833,527$) was 14% (95% CI 4 to 23%) [8,9], and the frequency of PNES among those with epilepsy was 17% in a single study [9].

3.2. Demographic features

There were no differences between those with dual diagnosis, PNES, and epilepsy in the aspects of age, age at disease onset, disease duration, sex, marital, or educational status (see Table 1).

3.3. History details

Patients' history of physical or sexual abuse, abuse in childhood, significant head trauma, and substance abuse, was similar among patients with dual diagnosis and PNES in all five studies [12,17,47,56,72] that reported this. It did not differ among patients with dual diagnosis and epilepsy in two [17,72] out of three studies [17,26,72].

3.4. Seizure characteristics and medication

Nonepileptic seizure characteristics were assessed in ten studies with eight finding differences in semiology of seizures between those with PNES and dual diagnosis. Stiffening of the body (60% vs. 37%, $p > 0.05$) [12], opisthotonus (18.5% vs. 0%, $p > 0.03$) [56], convulsive behavior (85% vs. 55.5%, $p > 0.05$) [47], right-hemibody PNES events (7% vs. 23%, $p = 0.054$) [77], autonomic symptoms/signs during the seizure (51.6% vs. 23.7%, $p = 0.03$) [27,99], and postictal state (84% vs. 58%, $p = 0.02$) [12] were more common in patients with PNES than those with dual diagnosis. Total lack of responsiveness (63% vs. 25%, $p < 0.05$) [18] and myoclonic seizure semiology (10% vs. 2%, $p = 0.073$) [77] were observed more often in patients with dual diagnosis than in those with PNES. Absence/staring seizures were less common in dual diagnosis in comparison with patients with epilepsy (9% vs. 41%, $p = 0.003$) [77].

The median seizure frequency was significantly higher in patients with dual diagnosis than in those with PNES (for instance 30 (range: 2 to 500) vs. 125 (range: 1 to 1000) seizures per year [47]) in two [31,

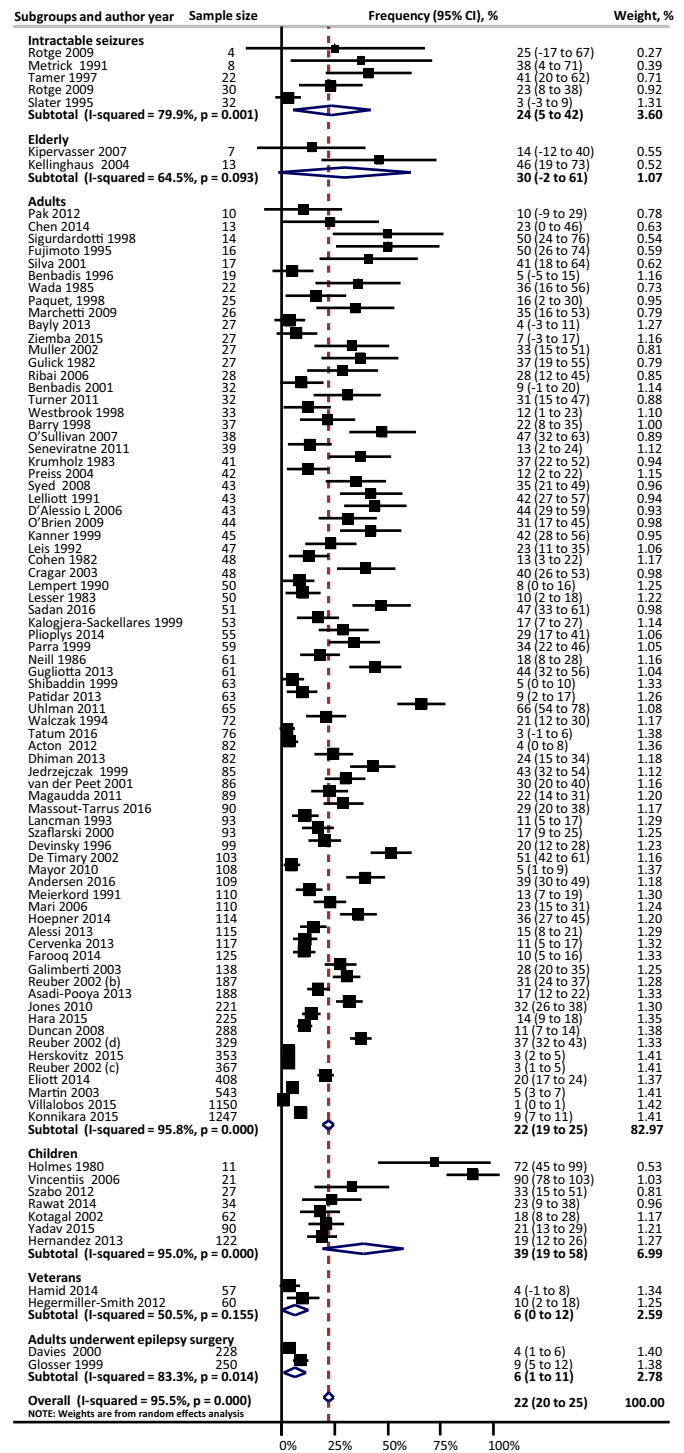


Fig. 2. The frequency of epilepsy in patients with PNES.

47] of three studies, but, in one study, this held only before the diagnosis of PNES [47].

As expected, patients with dual diagnosis had higher antiepileptic drug (AED) use than patients with PNES (5 studies [17,33,47,40,126]) and in one study, lower AED use than in those with epilepsy [17]. Patients with PNES took more psychotropic drugs than AED in one study [33].

3.5. Miscellaneous clinical features

Two studies explored possible association between dual diagnosis and medical comorbidities. One study ($n = 689$) showed that patients

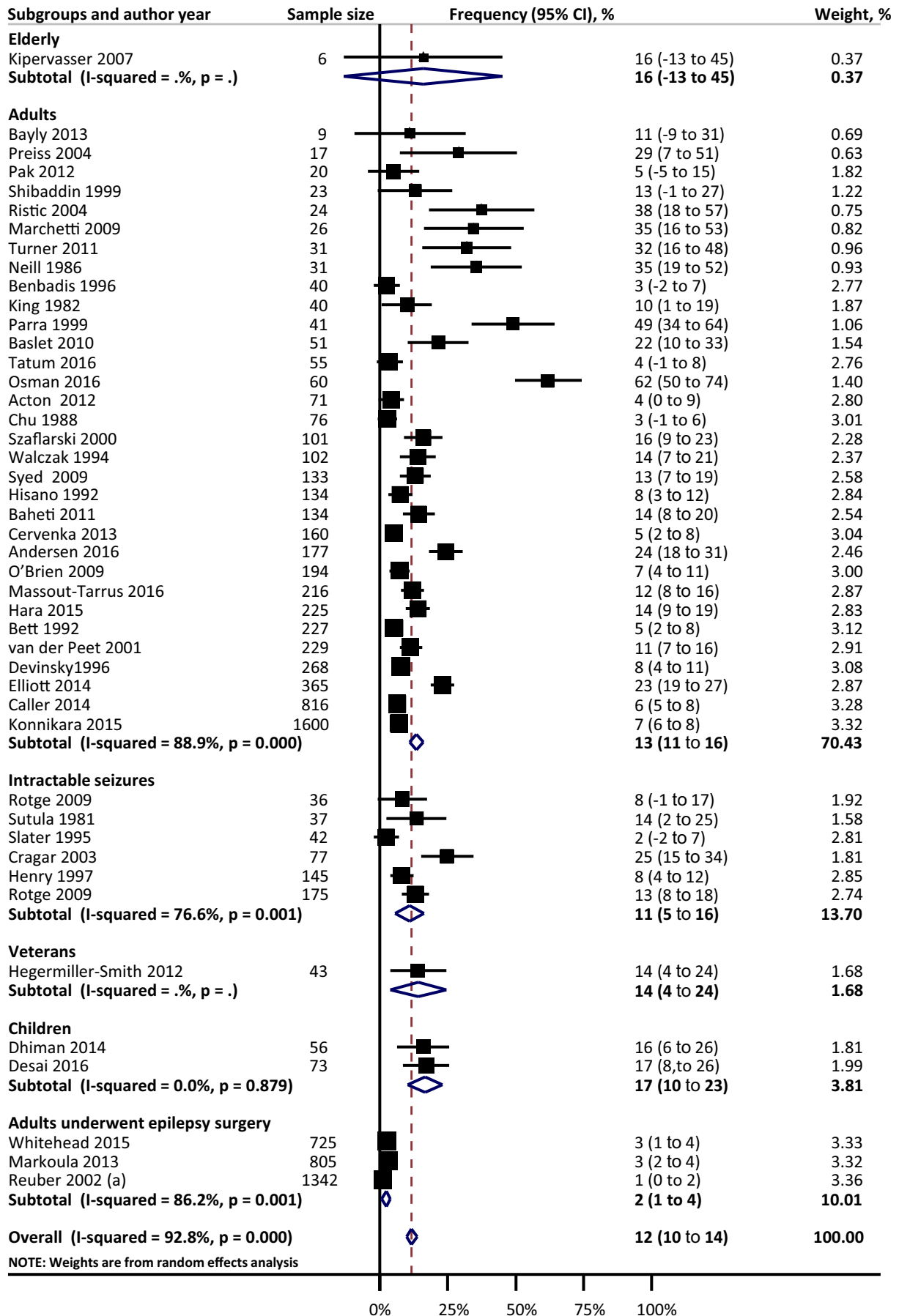


Fig. 3. The frequency of PNES in patients with epilepsy.

Table 1
Age, sex, age, disease duration, and education level in patients with dual diagnosis in comparison with those with PNES and/or epilepsy.

	D'Alessio et al. [18]	Mari et al. [40]	Kuyk et al. [58]	Asadi-Pooya and Emami [12]	Hara et al. [31]	Hoepner et al. [33]	O'Sullivan et al. [47]	Sadan et al. [56]	Cragar et al. [17]	Elliott and Charyton [26]	Galimberti et al. [27]	Jovik ^b [87]	Reuber et al. [62]	Markoula et al. ^a [89]	Konnikara et al. [88]	De Timary et al. [20]	Duncan and Oto [25]	Turner et al. [72]	Wissel et al. [77]	Glosser et al. ^a [28]
Total N in the study	43	110	85	188	225	114	38	51	106	689	138	71	180	805	2735	103	288	53	138	250
N PNES	24	85	60	156		73	20	27	29	324	31	17			1488	50	257	22	46	228
N Epilepsy	–	–	–	–	194				58	281	69	30	90	779	1135			21	46	
N Dual	19	25	25	32	31	41	18	24	19	84	38	24	90	26	112	53	31	10	46	22
Age	<	<	>	=	= ES	=	=	=	= ES	= ES	=	=	= ES							
Age at onset		=	=		= ES	<	=	=	<	= ES	>	= ES	= ES			<	<	=	= ES	> ES
Male	>	=	=	=	=	=	=	=	= ES	< ES	=	=	< ES	< ES	<	=				< ES
Disease duration	<PNES	>PNES			= ES	<PNES			< ES	< ES	=	=	< ES	< ES					=	> ES
Education level		=	=	=	< ES				=	= ES	= ES	= ES	>					=		=

"<" Denotes those with dual diagnosis are younger than those with PNES or lower proportion of males among those with dual diagnosis than those with PNES.

"=" Those with dual diagnosis are at same age/gender balance/disease duration/education level as those with PNES.

">" Those with dual diagnosis older/more males than those with PNES.

"< ES" Those with dual diagnosis younger/fewer males/had shorter disease duration than those with epilepsy.

"= ES" Those with dual diagnosis same age/gender balance/disease duration/education level was lower as those with epilepsy.

"> ES" older/disease duration longer in those with dual diagnosis than in epilepsy.

"> PNES" education level was higher/disease duration was shorter in patients with PNES than with dual diagnosis.

"< PNES" disease duration was shorter/education level was lower in patients with dual diagnosis than with PNES.

^a Included patients who had undergone resective epilepsy surgery.

^b Studies recruiting children.

Table 2
Comparative analysis of epilepsy location in patients with dual diagnosis and epilepsy.

Study	N/N ^a	Dual diagnosis	Epilepsy
Pillali and Haut [59]	38/78	Frontal lobe	Temporal lobe
Konnikara et al. [88]	112/1488	No difference ^b	
Wissel et al. [77]	46/46	Right hemisphere	–
Reuber et al. [62]	90/90	No difference ^c	

^a Number of patients with dual diagnosis/epilepsy.

^b Temporal lobe epilepsy was diagnosed in 79% (dual) and 75% (epilepsy) respectively.

^c More generalized epileptiform interictal changes were registered in patients with dual diagnosis.

with dual diagnosis in comparison with those with epilepsy more often smoked, suffered from pain, asthma, gastroesophageal reflux disease, and migraine while another one (n = 188) [12] reported no association.

In one small study (n = 20), the authors suggested an interesting way of classifying patients with dual diagnosis into three groups: i) resistant epilepsy with anxiety/depression and normal cognition, ii) learning difficulties and dependent personality, and iii) comorbid cluster B personality disorders, anxiety disorders, psychic trauma, and normal cognition. However, the small numbers meant this was only a hypothesis-generating study [4].

3.6. EEG and neuroimaging

As expected, patients with dual diagnosis, in comparison with those with PNES, more often had abnormalities on EEG [33,61,91,109]. They were less susceptible to EEG induction procedures in one study [40]. Temporal lobe epilepsy was equally common in patients with epilepsy and dual diagnosis according to the biggest study of its kind (n = 1488) [88] while smaller studies yielded conflicting results (Table 2).

3.7. Psychiatric comorbidity and neuropsychological features

Most researchers used DSM-IV criteria for diagnosing psychiatric comorbidities [18,47,72], however, there was no consistent approach across researchers to the assessment or categorization of neuropsychological features. At most, specific neuropsychological features were explored in no more than three studies, making an overall summary difficult.

Generally, researchers did not find a difference between PNES and dual diagnosis in psychiatric morbidity [47,56,72] or suicide attempts [18]. In three studies, patients with PNES and dual diagnosis experienced more behavioral problems than patients with epilepsy [27,49,84].

Compared with patients with PNES, patients with dual diagnosis more often experienced affective and personality disorders [26,58] but less often had posttraumatic stress disorder (PTSD) and dissociative disorder [18,58] (Table 3). Using the Minnesota Multiphasic Personality Inventory, patients with dual diagnosis, compared with patients with epilepsy, scored more highly on the 'hysteria' [17,86,122], 'lassitude-malaise', and 'mental dullness' scales [17]. On 'hypochondriasis' and

'depression' scales, they scored lower than patients with PNES in one study [86].

Five studies [25,62,72,87,91] assessed cognitive function in patients with PNES and/or epilepsy and dual diagnosis and yielded conflicting results. Two out of four studies reported significant differences in cognitive functions between patients with PNES and dual diagnosis [87,91]; two found that cognitive changes could predict coexistence of PNES in epilepsy [25,62] while one reported similar cognitive status for patients with dual diagnosis, PNES, and epilepsy [72].

3.8. Employment and disability status

Employment status did not differ among patients with dual diagnosis and PNES in two studies [47,58]. Disability status and length of medical care for the seizure disorder were analyzed in four studies, which yielded conflicting results [17,26,77,126].

3.9. Outcomes in patients with dual diagnosis

Unfavorable outcomes in the group with dual diagnosis were reflected in a greater number of emergency department visits in comparison with epilepsy [15] and more frequent hospital visits [56] and rarer achievement of remission than in those with PNES [78].

Two studies demonstrated that detection of dual diagnosis could improve subsequent outcomes in those patients [13,56]. After diagnosis of PNES, psychogenic events more often ceased in the group with dual diagnosis as opposed to the group with PNES in one study (22% vs. 58%) [56].

4. Discussion

Dual diagnosis is more frequent in this systematic review than previously reported [3]. This could be explained partly by the recruitment of patients in most studies from specialized epilepsy centers where complex and unusual cases concentrate. However, this relatively high frequency of dual diagnosis was also shown in two population-based studies suggesting that it is also common in overall populations of patients primarily diagnosed with epilepsy or PNES.

The lowest frequency of dual diagnosis was registered in surgical series (2%) which is probably explained by careful presurgical examination and exclusion of most of the patients with comorbid PNES. In contrast, the highest frequency of dual diagnosis was observed among patients referred to (neuro)psychiatry/neuropsychology units (42%), which probably reflects factors leading to referral to those services. This finding emphasizes the importance of considering the recruitment setting when looking at comorbidities.

Dual diagnosis was almost twice as frequent in the studies recruiting people with PNES than in the studies recruiting those with epilepsy. It could be that a certain proportion of the patients with epilepsy developed PNES, which then predominated in the clinical picture; such a pattern is common in our experience.

Table 3
Psychiatric comorbidities in patients with dual diagnosis, PNES, and epilepsy.

Study	Dual	PNES	Epilepsy	Findings
Sadan et al. [56]	24	27		PNES = dual diagnosis
Turner et al. [72]	10	22	21	ES = PNES = dual diagnosis
O'Sullivan et al. [47]	18	20		PNES = dual diagnosis
Wissel et al. [77]	46	46	46	ES < dual diagnosis; PNES < dual diagnosis depression, anxiety and stressor as a trigger of a seizure
Helmstaedter [84]	335			Dual diagnosis > ES general behavioral problems
Owczarek [49]	152			Dual diagnosis > ES anxiety and neuroticism
Ito et al. [57]	165			Dual diagnosis > ES dissociation
Elliott and Charyton [26]	84	32	281	Dual diagnosis > PNES as depression, anxiety, bipolar disorder, and personality disorder
Kuyk et al. [58]	25	60		Dual diagnosis > PNES personality disorders; Dual diagnosis < PNES somatoform disorder
D'Alessio et al. [18]	19	24		PNES = dual diagnosis

Demographic features of patients with dual diagnosis, PNES, and epilepsy were similar. Despite some differences in individual studies, no consistent or specific semiological signs of dual diagnosis were found which may differentiate it from patients who had PNES or epilepsy alone.

Varying findings on psychiatric comorbidities and neuropsychological correlates in patients with dual diagnosis reflect the clinical heterogeneity of this phenomenon. On the other hand, only some authors performed formal psychiatric evaluation to assess psychiatric comorbidities while the rest used only psychometric scales, which could be considered as a limitation of those studies. There are several potential overlapping mechanisms of the development of PNES in epilepsy. These include a) anxiety and other psychiatric comorbidity arising from the experience of epilepsy; b) the way in which epilepsy may act as a 'symptom scaffold' on which is built a recurrent conditioned response to arousal [2]; c) as an involuntary substitute symptom especially in a population with intellectual disability and after successful surgery for epilepsy. In the latter, case reduction in epileptic seizure frequency leads to the development of PNES driven by secondary gains such as caregiver attention or activity avoidance [4]. The development of PNES after epilepsy surgery could be not only "compensatory" but also a result of psychological stress associated with the operation [60, 63].

Very few studies assessed outcomes in patients with dual diagnosis. Some data showed that dual diagnosis predisposes patients to worse outcomes, but once the correct diagnosis is made, the number of events and number of AED is likely to decrease. This emphasizes the importance of timely diagnosis of PNES in patients with epilepsy.

In clinical practice, the data suggest that patient with treatment-resistant epilepsy is at higher risk of developing PNES, and vice versa. The dual diagnosis should be considered in the cases of the unexpected development of new seizure types or increase in their frequency. Correctly identifying dual diagnosis is typically harder than isolated PNES and especially recording both types of events on VEM. In some cases, details from the patient's history can be misleading. For instance, mild traumatic brain injury is a risk factor for the development of not only epilepsy but also posttraumatic stress disorder and PNES [127]. On the other hand, although stress and adverse experience are considered established risk factors for the development of PNES in some individuals, they can also contribute to the development/exacerbation of epilepsy [128,129].

This systematic review had several limitations. We included studies regardless how PNES, epilepsy, and dual diagnosis were identified. In the majority of cases, the diagnosis was confirmed by VEM while some authors used more relaxed diagnostic criteria. There was a high degree of heterogeneity between the studies that even a random effects meta-analysis may not have compensated for. Nonetheless, we think the meta-analysis has some face validity in describing the published literature although summary values should be interpreted with caution. We also did not evaluate publication bias. There are likely to be other series of patients with ES, where PNES was not a focus of the study title or abstract but it is recorded as a comorbidity. We were not able to analyze studies in relation to the frequency of intellectual disability within individual studies, as these data were rarely available. Clinical experience suggests that patients with intellectual disability have a particularly high rate of dual diagnosis. Methodological limitations of some studies could also affect the dual diagnosis. For instance, provocative tests (verbal suggestion, saline injection) were used in 2 studies during VEM, and in some studies, the 'criteria for epileptiform discharges' were not clearly described. None of the studies presented a priori power calculations for the sample size.

Future research could attempt to build on the categorization of patients with dual diagnosis of PNES and epilepsy under different subtypes depending on mechanisms of development and clinical features. Thus far, there is no work studying effective treatment of PNES in those with dual diagnosis as they tend to be excluded from clinical trials of

AEDs. Clinicians working in this area tend to adopt a model of treatment, which focuses on helping patients and their family identify individual seizure types and then treat accordingly. An additional element of therapy in those patients can involve a focus on understanding the hypothesized mechanisms of association described above. Psychogenic nonepileptic seizures are so common in certain patients with epilepsy (those with cognitive decline, affective disorders etc.) that it begs the question of whether preemptive education or psychological interventions are warranted and may be helpful in those high-risk groups?

5. Conclusion

Dual diagnosis is relatively common among those diagnosed with PNES or epilepsy, especially in those who referred to specialized epilepsy centers. This indicates the importance of considering this comorbidity, not only in patients with PNES but also in a population with epilepsy. Future research should pursue potential mechanisms of the development of PNES in epilepsy, describe individual risk factors and test possible interventions for the treatment and possibly early detection and prevention of the development of PNES in patients with epilepsy.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.yebeh.2018.10.010>.

Conflict of interest

None of the authors have any conflict of interest to disclose.

Acknowledgments

During the completion of this work, Ying Xu held the University of Sydney Postgraduate Award, Maree L. Hackett held a National Heart Foundation Future Leader Fellowship, Level 2 (100034, 2014–2017) and a National Health and Medical Research Council Career Development Fellowship, Level 2 (APP1141328 2018–2021); Jon Stone was supported by a National Research Scotland Career Fellowship.

The authors want to thank the following researchers at the George Institute for their language assistance: Brendan Smyth (Italian), Laurent Billot (French), Veronika Olajcova (Czech), Zeljka Calic (Serbian), Cindy Kok (Dutch), and Sohei Yoshimura and Toshiaki Ohkuma (Japanese). The authors also thank Jayne O'Hare, a librarian from the University of Sydney for her assistance in building up the searching strategies.

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