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Economic Cost of Functional Neurologic Disorders: A Systematic Review

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Abstract

Introduction

Functional Neurological Disorder (FND) represents genuine involuntary neurological symptoms and signs including seizures, weakness and sensory disturbance which have characteristic clinical features, and represent a problem of voluntary control and perception despite normal basic structure of the nervous system. The historical view of FND as a diagnosis of exclusion can lead to unnecessary healthcare resource utilisation, and high direct and indirect economic costs. A systematic review was performed using PRISMA guidelines in order to assess these economic costs, and to assess for any cost-effective treatments.

Methods

We searched electronic databases (Pubmed, PsycInfo, Medline, EMBASE, and the National Health Service Economic Evaluations Database of the University of York) for original, primary research publications between inception of the databases and 8th April 2022. A hand-search of conference abstracts was also conducted. Key search terms included "functional neurological disorder", "conversion disorder" and "functional seizures". Reviews, case reports, case series and qualitative

studies were excluded. We performed a descriptive and qualitative thematic analysis of the resulting studies

Results

The search resulted in a total of 3,244 studies. 16 studies were included after screening, and exclusion of duplicates. These included: cost-of-illness (COI) studies which were conducted alongside cohort studies without intervention, and included a comparator group, e.g. another neurological disorder (n=4); COI studies which were conducted alongside cohort studies without intervention, and which did not include a comparator group (n=4); economic Evaluations (EE) of interventions which were either pre-post cohort studies (n=6) or randomized controlled trials (n=2). Of these, five studies assessed active interventions, and three studies assessed costs before and after a definitive diagnosis of FND.

Studies showed an excess annual cost associated with FND (range $4,964 to $86,722 2021 USD), which consisted of both direct, but also large indirect costs. Studies showed promise that interventions, including provision of a definitive diagnosis, could reduce this cost (range 9% to 90.7%). No cost-effective treatments were identified. Study comparison was limited by study design and location heterogeneity

Conclusion

FND is associated with significant use of healthcare resources, resulting in economic costs to both the patient and the tax-payer, as well as intangible losses. Interventions, including accurate diagnosis, appear to offer an avenue towards reducing these costs.

Background

Functional Neurological Disorders (FND) represents genuine involuntary neurological symptoms and signs which have characteristic clinical features and represent a problem of voluntary control and perception despite normal basic structure of the nervous system [1]. Manifestations of FND are varied and include in isolation or combination: abnormal movements; weakness or paralysis; sensory loss or abnormal sensory symptoms; swallowing or speech symptoms; and epileptic-like episodes, i.e. functional seizures [FS]) [1]. FNDs carry a significant impact on their sufferer's quality of life [2,3], and patients often present with comorbid psychiatric conditions, with both depression and anxiety occurring in up to 40% of FND patients [4,5].

FND has a prevalence of up to 50/100,000, and an incidence of up to 12/100,000/year. PNES contributes a further 1.5–4.9 per 100,000 population per year, with a prevalence of 2–33 per 100,000 population [6]. Patients with FND make up 9% of neurology admissions [7,8], 16% of neurology clinic referrals [9], and 10-25% of patients referred to epilepsy specialist centres [10]. Patients with FND often require multiple consultations over several years before receiving a diagnosis of FND [11], and then frequently re-present to Emergency Departments after receiving such a diagnosis [12]. Delayed diagnosis leads to worse outcomes for patients [4], as well as preventable costs, such as missed work, GP and specialist appointments, and investigations. Diagnostic uncertainty amid ongoing symptoms can also lead to intangible costs, such as decreased Quality of Life (QOL).

These costs carry a burden to patients, clinicians, and healthcare systems, as well as to the economy. Indeed, FND patients have been found to be more likely to not be working for health reasons, and more likely to be receiving disability-related state financial benefits than people with other neurological disorders [13].

Various treatments, such as physiotherapy [14] or CBT [15] can lead to improvement of these symptoms and QOL. Importantly an intervention of simply providing the patient with an accurate diagnosis, and thus explanation of their symptoms, can also improve mood and QOL [16], and decrease healthcare resource utilisation [17].

The costs of FND (and other medical conditions) can be thought of as direct and indirect costs. Direct costs represent resources utilised for health care (e.g. cost of investigations, or the time spent on assessment by a doctor), while indirect costs represent productivity losses arising from morbidity-related sickness absence (e.g. loss of employment, benefits, or the cost of childcare while hospitalised). Direct and indirect costs together constitute the economic burden of FND, which can be quantified via cost-of-illness studies (COI). A COI study can use a top-down (TD) or a bottom-up (BU) approach. Bottom up methods estimates costs based on data from records (or observed usage) at the service provider level, whereas top-down approaches utilise administrative registers of costs[18].

Other studies of health care utilisation focus on economic evaluation. There are different types of Economic Evaluations (EE): cost-minimization analyses (CMA) address the question of whether an intervention would result in lower health care costs. Cost-effectiveness analyses (CEA), combine costs and clinical parameters, such as gained life years or recovered cases, to assess whether the intervention is cost-effective [19]. Cost-utility analyses utilise quality-adjusted life years (QALYs) as their measure of effectiveness. QALYs attempt to quantify the impact of the patient's condition on the quality and quantity of life lived. Typically, cost-effectiveness analyses utilise the Incremental Cost-Effectiveness Ratio (ICER), which is a measure of the additional cost per unit of health gained. Whereas COI present information only on the economic burden of a disease, EE can assist decision makers to decide towards which interventions to prioritise resources.

Objectives

Given the reportedly high burden FND places on patients and society, we aimed to systematically review the health economic literature on FND. Our objectives were:

1. To investigate the direct and indirect costs of Functional Neurological Disorders
2. To investigate whether any interventions to treat Functional Neurological Disorders are cost-effective

Methods

Criteria for considering studies for the review

This study followed the methodology and guidelines set out by the PRISMA (Preferred Reporting Items for SysteMAtic reviews) checklist for systematic reviews [20] **(eAppendix 1)**. Studies were included if they reported original cost or cost-effectiveness data for functional neurological disorders. The references of any studies whose text was read in full were screened to identify further studies. Reviews, qualitative studies, studies reporting results of other studies, qualitative

studies and any studies which were not available in English were excluded. Case reports and series were also excluded. Papers were screened for inclusion by the BOM and MY, and all data was extracted by BOM. When a single study was published in several papers, the article reporting the largest group was used.

No restrictions on age, gender, or treatment level were applied.

Outcome measures

The primary outcome measures were the monetary and non-monetary costs of FND to patients and the economy.

Search methods for identification of studies

Searches were made in April 2022 from inception of the databases to 8th April 2022 in the following electronic databases: PubMed, EMBASE, Medline, PsycINFO, and the National Health Service Economic Evaluations Database of the University of York as well as in the reference lists of identified studies. These databases contain a comprehensive list of medical literature and reports.

The following search string was used (in titles and abstracts):

("conversion disorder" OR "conversion reaction" OR psychogen* OR non-epileptic OR nonepileptic OR hysteri* OR "functional neurological" OR "functional movement" OR "functional motor" OR "functional tremor" OR "functional sensory" OR nonorgan* OR non-organ* OR Astasia-Abasia OR "Astasia Abasia") AND (QALY OR “quality adjusted life year$” OR “disability adjusted life year$” OR DALY OR cost OR expense OR expenditure OR out-of-pocket OR economic OR budget OR monetary OR resource* OR consumption OR informal care)

The subject heading of conversion disorder was exploded on the Ovid platforms (Psycinfo, Medline, and EMBASE). The following conference proceedings during the past five years were hand searched: Society of Biological Psychiatry, American Psychiatric Association, The British Neuropsychiatry Association, Royal College of Psychiatrists, Association of British Neurology, American Academy of Neurology. Abstracts which were identified as meeting the inclusion criteria for the review had their full texts sought for assessment. BOM contacted the lead author of any papers found through this method.

Data collection and analysis

A record of included and excluded studies (and reasons for exclusion) were kept. Data was extracted using the DistillerSR software [21] by BOM, and included study characteristics, demographics, and as economic costs such as direct healthcare and non-healthcare costs, indirect costs, and QALY measurements.

A meta-analysis was not deemed appropriate given the significant heterogeneity in the studies’ cohorts, location (differing healthcare systems), costs included, and cost-data sources. In order to compare results for the non-comparator studies, costs per patient were transformed using Purchasing Power Parities (PPP) for Gross domestic product to US Dollars (USD) [22].The cost data of studies using year of price level before 2021 were inflated by 1 percent annually in order to calculate a common end value for the year 2021. If means and/or standard deviations were not reported,

freely available software was used (Window Ruler) to calculate these measures from the provided graphs.

Assessment of paper quality

Assessment of the overall methodological quality of economic evaluations was informed by application of the Scottish Intercollegiate Guidelines Network (SIGN) Methodology checklist [23] (**eAppendix 2)**, as well as a checklist of methods (**eAppendix 3**). Distiller SR was used to produce quality figures based on our assessment as low, acceptable, or high quality.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was registered was registered on PROSPERO on 8th April 2022, registration number *CRD42022322142*

Ethics was not sought as any data collected was obtained from publicly accessible documents.

Data availability

Individual researchers may request collected data from the corresponding author

Results

Search results are shown in the **Figure**. 58 studies were reviewed in full text, of which 16 studies were included. Four conference abstracts were identified, and their data requested from their respective authors, of which one responded. 42 studies were excluded for reasons detailed in the **Figure**.

Study Quality

Of the included studies, four (Stephen *et al* [24], Goldstein *et al* [25], Jennum *et al* [26], and Luthy *et al* [27]) were deemed to be of high quality, ten were deemed to be of acceptable quality (Deleuran *et al* [28], Nelson-Sice *et al* [29], Tinazzi *et al* [30], Seneviratne *et al* [31], Martin *et al* [32], Ahmedani *et al* [33], Russell *et al* [34], Magee *et al* [35], Nielsen *et al* [36], Reuber *et al* [37]) and two were deemed to be of low quality (Chemmanam *et.al* [38], Goyal *et al* [39]).

Study Characteristics

General study characteristics are presented in **Tables 1, 2, and 3**. The earliest study was published in 1998, the most recent in 2021. Of the included studies on COI of FND, 81% (n=13) were published in the year 2013 or later, which perhaps indicates that the COI of FND is a topic of recent and increasing interest. Sample sizes varied from 11 to 64,138. Five studies were conducted in the USA, four in Great Britain, two in Denmark, and one in each of Italy, Ireland, Australia, Canada, and India. Ten studies focused on FS, four studies focused on FND / Conversion Disorder, and two studies focused on Functional Movement Disorder (FMD).

Studies were also heterogenous in terms of diagnostic criteria. Of the six studies of FND/FMD one used ICD 9/10 (Stephen *et al* [24]), one used Gupta and Lang Criteria (Tinazzi *et al* [30]), one used Fahn Williams criteria (Nielsen *et al* [36]) and three used consensus diagnosis (Nelson-Sice *et al* [29], Goyal *et al* [39], Reuber *et al* [37]). Of the studies of FS, six used the gold standard of Video EEG (Goldstein *et al* [25], Deleuran *et al* [28], Russell *et al* [34], Chemmanam *et al* [38], Seneviratne *et al* [31], Martin *et al* [32]), two used

ICD 9/10 (Jennum *et al* [26], Luthy [27]), one used both ICD 10 and vEEG (Ahmedani *et al* [33]) and one study's diagnostic criteria were unclear (Magee *et al* [35]).

Study designs were made up of three types:

1. COI studies which were conducted alongside cohort studies without intervention, which included a comparator group, i.e. another neurological disorder (n = 4) [24,26,27,39]

2. COI studies which were conducted alongside cohort studies without intervention, which did not include a comparator group. (n = 4)[29-31,35]

3. Economic Evaluations (EE) of interventions which were either pre-post cohort studies (n = 6)[28,32-34,37,38] or randomized controlled trials (n = 2)[25,36]. Of these, five studies assessed active interventions, and three studies assessed costs before and after a definitive diagnosis of FND

eAppendix 4 displays the cost categories considered. Studies varied in terms of the detail of their breakdown of costs. Eight studies assessed only hospital costs (inpatient and specialist outpatient services), with seven of these studies focused only on hospital in-patient costs. Only four studies assessed medication costs outside of hospital. Three studies assessed productivity losses to the patient and informal carers resulting from their FND, while Jennum *et al* [26] assessed productivity loss in terms of cost to the state. Studies also varied in regards to their reporting of cost data. Although authors reported including different types of costs in their analysis, some did not give exact figures for these individual costs. **eAppendix 5** details what costs were explicitly reported, by paper. Two papers gave only the total overall cost per patient.

Population Demographics.

13 studies investigated the costs of adults only, and two studies (Stephen *et al* [24] and Jennum *et al* [26] included both adults and minors with FND. Luthy *et al* [27] investigated the costs at a paediatric hospital. Adult patients mean/median age in studies ranged between 35 [25,31] and 45.48 [24], and every study which noted gender ratio reported a majority of female patients, ranging from 57% [34] to 86% [28].

Economic costs

Summaries of the findings are given in **Tables 1, 2, and** 3. Several summary results can be derived from the economic data presented in the selected papers.

Firstly, eight studies assessed costs before/after an intervention, where intervention was defined as psychological based treatments or making and communicating a robust diagnosis. Each of these eight studies showed cost reduction, or improved QALYs, in the period after the intervention. Goldstein *et. al* calculated the incremental cost of CBT and Standard Medical Care as £120,658 per QALY compared with Standard Medical Care alone. This fell above the threshold for cost-effectiveness required by the National Institute for Health and Care Excellence (NICE) of under £20,000 to £30,000 per QALY [40]. Nielsen *et al*'s [36] pilot Randomised Control Trial (RCT) of a physiotherapy intervention for patients with FMD reported a mean incremental cost per QALY gained of £12,087 [36], while Reuber *et al*'s [37] uncontrolled pilot study reported a mean incremental cost per QALY gained of £5,328 (if QOL improvements lasted 1 year) for a brief psychodynamic intervention in patients with mixed functional neurological symptoms [37].

Secondly, in those studies that compared FND costs to other chronic neurological diseases, costs are similar. Both Luthy *et al* [27], and Stephen *et. al* [24]showed a lesser cost-burden of PNES compared to epilepsy, although the latter study showed greater cost in emergency settings, despite the fact that Stephen *et al* [24] included only refractory epilepsy as a comparator. The only study which compared the economic costs of FND patients to healthy controls (Jennum *et al* [26]), showed a marked increase in costs to both FND patients and their carers.

Thirdly, in those studies which gave estimates of total costs to the taxpayer, Stephen *et al* [24], Tinazzi *et al* [30], and Magee *et al* [35] give estimates of the total cost of illness to their countries of $1,200,000,000 USD (hospital charge costs for all FND subtypes and all ages), €34,500,000 (direct health costs for functional motor symptoms in over people over 16 years of age), and €19,525,629 and €48,289,190 (direct and indirect costs for functional seizures in adults) per annum, respectively.

Finally, overall costs vary significantly due to the studies' methodological and geographical heterogeneity; after costs were adjusted to Purchasing Power Parities (PPP) for Gross domestic product, mean annual costs per patient of PNES range from $4,964 2021 USD (Luthy *et al)* [27] to $83,884 2021 USD (Goldstein *et al*) [25], while those of functional neurological disorders range from $21,433 2021 USD (Tinazzi *et al*) [30] to $86,722 2021 USD (Nelson-Sice *et al*) [29].

Discussion

To our knowledge, this is the first systematic review of health economic studies for functional neurological disorders. Our findings indicate two trends: firstly, that FND causes costs per patient, comparable with, or in excess of, other chronic neurological disorders with similar symptoms (e.g. FS vs epilepsy). Secondly, that interventions (including making and delivering a robust diagnosis) have the potential to improve patients' health status (measured in both QALYs and symptom relief) and reliance on healthcare resources, with subsequent reduction of costs. However, the heterogeneity of studies provides challenges in interpreting and comparing results.

There was significant variation in reported costs, possibly resulting from heterogeneity in diagnostic practices, differences in types of costs included, cost data sources, and study location. After costs were adjusted to Purchasing Power Parities (PPP) for Gross domestic product, mean annual costs ranged from $4,964 2021 2021 USD (Luthy *et al)* [27] to $86,722 2021 USD (Nelson-Sice *et al*) [29]. This heterogeneity of costs is also reflected in systematic reviews of the economic costs of Medically Unexplained Symptoms (mean annual costs ranging from $1,584 to $6,424 2006 USD from 1986 to 2004) [41], multiple sclerosis (mean annual costs ranging from $13,721 to $82,080 2012 USD from 1995 to 2012) [42], Epilepsy (mean annual direct costs ranging from £611 - €4,292 from 1992 to 2013)[43], and Treatment-Resistant Depression (mean annual costs ranging from $3,800 to $49,000 2006 USD from 2004 to 2014) [44].

This heterogeneity limits not only comparisons of studies included in this review, but also the comparison of the economic cost of FND with the economic costs of other chronic, neurological, and psychiatric disorders. However, two high quality studies included in this review (Stephen *et al* [24] and Luthy *et al* [27]) reported FND and FS respectively as having a similar mean direct costs per patient as epilepsy. Stephen *et al* [24] also reported a similar mean direct cost per adult patient admitted with FND as with demyelinating disorders. Given that FND patients have levels of physical disability equivalent to people with multiple sclerosis or epilepsy, and higher frequencies of psychological comorbidities than those two disorders [13], one might expect similar or greater indirect and

intangible costs. This provides powerful insight into the economic impact of a disorder which has relatively limited awareness in the medical community [45,46].

Given the high prevalence of comorbidities which occur in patients with FND [4,5], it is possible that these comorbidities might have contributed to the costs calculated by the papers included in this review. This lack of adjustment would have led to inflated costs being calculated for the FND cohort [47]. Luthy et al attempted to isolate the pure economic cost of FND through use of an extensive exclusion criteria (of both medical and psychiatric comorbidities). The authors acknowledged that study of such a cohort likely lessened the external validity of their findings, given that the successful treatment of many chronic neurological disorders, and especially FND, requires a holistic approach.

In those studies which assessed economic effectiveness of interventions using QALYs there was significant variability. Part of this is due to differences in the patient population and interventions. However, in two studies the patient population and intervention were similar, namely patients with FS undergoing psychological based treatments. Despite this, there were significant differences in QALY costs. Goldstein *et al* [25] reported an incremental cost of CBT and Standard Medical Care as £120,658 per QALY compared with Standard Medical Care alone, while Reuber *et al* [37] reported mean incremental cost per QALY gained of £5,328. A number of factors are likely to contribute to these widely differing figures. Reuber *et al* [37] (N = 63) reported a unit cost of treatment as £213.15, while Goldstein *et al* [25] (N= 293) reported a unit cost of £1064. Furthermore, Reuber *et al* [37] based their analysis on clinical outcomes at 6 months, which they assumed would be the same at 12 months. If Goldstein *et al* [25] were to use clinical outcomes at 6 instead of 12 months, the cost per QALY gained would be lower as there was a greater quality of life difference at that time point, and a significant difference in the primary outcome measure of seizures. Finally, as Reuber *et al* [37] acknowledge, the lack of a control group in their study means that the cost-effectiveness of intervention cannot be regarded as proven in view of confounders such as placebo or regression to the mean effects. Moreover, the control arm in the Goldstein *et al* [25] study was not treatment as usual, but enhanced "standardised medical care", a package of care greater than what is typically provided for patients with FS, involving education and counselling from neurologists and psychiatrists. This in turn would have led to a smaller difference in QALY effects in the group, and therefore an underestimation of the cost-effectiveness of the intervention.

In studies without comparators, total costs varied from $18,549 to $43,661 2021 USD. Any conclusions reached from these studies is limited by their lack of a comparison group, and it is thus difficult to contextualise their reported findings.

Heterogeneity of study designs

A comprehensive COI study should include all direct and indirect healthcare costs, as well as intangible costs. The majority of studies in this review included only hospital-related costs. Such studies would underestimate the true economic cost of FND. Direct comparison of inpatient admissions costs was also limited by the difference in specific costs included in the studies, e.g. diagnostic imaging, medication, or multidisciplinary team consultations.

Heterogeneity of study location

Another complication of comparing costs from studies is their setting in different countries, and therefore different healthcare systems. Different countries have varying degrees of public healthcare systems, with patients carrying extra costs in more private systems. Such differences alter resource allocation by clinicians, and differences in healthcare systems have been shown to alter patients' use of healthcare resources [48].

Countries with more extensive social supports might also impact indirect costs. Jennum *et al* [26] identified that, compared with control subjects, a greater proportion of people with FS and their partners received social services benefits, such as sick pay or disability pension and housing benefits. The authors reported that, because of these public services, early retirement may be more common. Studies which assessed productivity loss ([20], [35], [25], [29]) reported that these costs of dwarfed those of direct costs. Productivity loss is likely to vary across countries, and thus impact differently on the overall economic cost of FND.

Implications for clinical practice

The studies in this review demonstrated the high cost of undiagnosed FND, and the reduction of this cost with diagnosis. This highlights the importance of establishing an early diagnosis of FND. The possible reasons for this are twofold; minimisation of excessive investigations and inappropriate medications [9], lessening the direct and indirect economic costs associated with both, while also minimising harm to the patient; improvement of their prognosis after careful communication of a clear and robust diagnosis [e1]. However, none of the studies reviewed have been able to discriminate between these two possibilities. The studies identified in this study suggest that this particularly applied to those patients with FS who receive a gold standard diagnosis by way of video-EEG. In those studies that assessed treatment interventions, costs were significantly reduced after the treatment intervention, but the evidence for the cost effectiveness of those interventions is currently more limited.

Implications for future research

Future research in this area should ideally include a comprehensive list of direct and indirect costs, in order to ascertain the full extent of the economic burden of FND. More studies from middle- and low-income countries, along with the inclusion of appropriate comparison groups would enable a comprehensive understanding of the global economic burden of FND.

To date, there has been no large studies showing cost-effectiveness of a treatment for FND, defined by NICE as a cost per QALY below $35,000 – $45,000 2009 USD across countries [e2]. To our knowledge, only Goldstein et al have thus far performed a comprehensive cost-effectiveness study, though costs were above NICE thresholds. Thus, rigorous cost-effectiveness studies should also be undertaken to investigate cost-effective treatments for FND. Similarly, studies should seek to distinguish the relative contributions to reduced costs after a diagnosis of FND, of the robustness of diagnostic communication, reduced inappropriate medical interventions or improved prognosis.

Limitations

As with other health economic systematic reviews, our review is faced with the limitation that studies which use top-down cost calculations would underestimate privately paid health care goods, while those utilising hospital charge data would, on average overestimate the true economic cost of the disorder twofold [e3].

This review highlighted a relative paucity of research into this topic. Four studies assessed indirect costs to the patient, and only three studies [25,36,37] included intangible costs. Productivity loss and intangible costs, such as cost associated with stigma, have been shown to make up a significant portion of the cost of epilepsy [e4], and their exclusion from the majority of studies in this review limits any estimate of the true burden of FND. The tertiary location of several studies meant that their population represented a severe subset of FND patients, and thus may limit the external validity of their findings. FND is a heterogeneous disorder, even in patients with the same symptoms.

Treatment approaches based primarily on the presenting symptom without consideration of other co-morbid problems may therefore dilute or even obscure treatment benefit for a subset of patients. This may in turn increase the associated costs per QALY of the intervention. Finally, the majority of comparator studies in this review used control groups with chronic neurological diseases (eg motor neuron disease, multiple sclerosis). Only a minority of such studies matched FND symptoms across groups, which should be an aim of future studies in order to understand relative costs more robustly (eg. comparison of costs of functional movement disorders with Parkinson's disease).

Conclusion

Functional Neurological Disorders are associated with significant use of healthcare resources, resulting in economic costs to patient and the tax-payer, as well as intangible losses. Given that functional neurological disorder is a medical condition like any other, we do not suggest that there should be zero cost associated with it. Rather, in this review, we have tried to explore how these costs can be moderated effectively with timely diagnosis and treatment. Interventions, including simply making a robust diagnosis, appear to offer an avenue towards reducing these costs. Significant heterogeneity exists between studies in this area, and we found a relative lack of research on indirect and intangible costs. Such costs appear to be high in Functional Neurological Disorders and offer a focus for further research, as do longer-term studies.

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Access eReferences at [LINK]

Author / Year / Country	Population	Condition	Number of patients	FND defined by	Costing method Source of cost data/ Currency	Costs Included	Intervention	Cost per patient before intervention	Cost per patient after intervention	% change from pre-to-post
Goldstein et.al [25] 2021 United Kingdom	Adults with dissociative seizures in the previous 8 weeks and no epileptic seizures in the previous year]	FS	368 total. Standardised medical care alone, n = 182; CBT+SMC, n=186)	vEEG and/or Clinical consensus	Bottom up CSRI questionnaire NHS records Average wage rates for value lost work and care provided by family/friends Medication costs: British National Formulary. QALYs: EQ-5D-5L, SFQ-6 2017/18 Great British Pound Sterling	Community services Medication costs Hospital based services Informal care Productivity Loss	CBT + Standardised Medical Care Standard Medical Care	**6 months before:** £29,066 **6 months before:** £33,261	**6 months after**: £29,320 **12 months after**: £52,933 **6 months after**: £22,828 **12 months after**: £55,503	**6 months**: 1% **12 months**: -9% **6 months**: -31.4% **12 months**: -16.6%
Deleuran et.al [28] 2019 Denmark	Patients with PNES offered psychotherapy by the specialized MDT at the Epilepsy Clinic, Rigshosptalet-Glostrup in Denmark, from 2010 - 2016	FS	242, 39 included in final analysis	Neurologist diagnosis +- vEEG	Bottom up Diagnosis-related group tariffs from the Danish Ministry of Health (provides data on average costs of healthcare services) Danish Krones, converted to Euro	ED visits, outpatient visits, and hospital admissions	CBT- or ACT-based interventions	**Months before Tx: Mean (SD) 24-13**: €2324 (4214) **12-0:** €5807 (6401)	**Months after Tx: Mean (SD) 0-12**: €1763 (4285) **13-24**: €1264 (3393), [median €64 (highly skewed)]	**1 year before/after** -69.6%
Russell et. al [34] 2016 Canada	Health Canada and the Public Health Agency of Canada databases	FS	28	Neurologist diagnosis & vEEG	Top Down Population Health Research Unit database Physician cost estimates: Calculated using $125 per hour for psychiatrist and family physicians $50 per hour for psychiatry residents, other students and health professionals Canadian Dollars	Hospital and physician cost and utilization data 1 year before and up to 3 years after ISTDP treatment	Intensive short-term dynamic psychotherapy (ISTDP)	$22,939.10	**Year 1**: $3,380.6 **Year 2:** $2136 **Year 3**: $4,462.6	**Year 1**: -85.3% **Year 2**: -90.7% **Year 3**: -80.5%

Author Year Country	Population	Condition	Number of patients	FND defined by	Costing method Source of cost data Currency	Costs Included	Intervention	Cost per patient before intervention	Cost per patient after intervention	% change from pre-to-post*
Ahmedani et.al [33] 2013 United States of America	Patients with a diagnosis of FS, who received services in the EMU, at Henry Ford Hospital from January 2006 - December 2008	FS	103. 24 members of HMO: allowed full collection of medical care costs - included in analysis	ICD 9	Top Down Southeastern Michigan HMO US dollars	Inpatient stays included psychiatric hospital admissions. Outpatient visits included neurology, behavioral health services (BHS), and other services (primary care or other specialty care)	Diagnosis with vEEG	Mean (SD): $4567.01 (4329.02) in **12 months** before diagnosis	Mean (SD): $2783.77 (3404.86) in **12 month**s after diagnosis	-39.10%
Chemmanam et.al [38] 2009 India	Patients who underwent inpatient vEEG during a 10-month period from September 2004 to July 2005 at Sree Chitra Tirunal Institute for Medical Sciences and Technology	FS	11 with comorbid epilepsy/FS. 8 with only FS	Consensus diagnosis and vEEG	Bottom up Medication: Local prices in INR Direct nonmedical costs: Patient interview Other data: unclear Indian Rupee	Direct medical costs: cost of AED therapy, diagnostic investigation, physician and hospital visits, and hospitalizations. Direct nonmedical costs: transportation charges to attend medical facilities for the patient and one caregiver.	Diagnosis with vEEG	INR 6985.70 ($174.60) in **12 months** before diagnosis	INR 964.3 ($2.43) in **12 months** after diagnosis	-86.20%
Martin et. al [32] 1998 United States of America	Patients diagnosed by the attending epileptologist on the UAB seizure monitoring unit at University of Alabama at Birmingham Epilepsy Centre	FS	20	Unclear	Bottom up Medication: Average price from pharmacy. Outpatient clinic: Outpatient Clinic administrative office. Diagnostic testing and ER visits: Hospital business administrative office. US Dollars	Medication usage, outpatient clinic visits, standard diagnostic testing (EEG, MRI, computerized tomography CT), laboratory testing (blood serum levels, AED levels), and emergency room visits	Diagnosis with vEEG (Cost of 6832 per patient)	$8156 in **6 months** before diagnosis	$1306 in **6 months** after diagnosis	-84%
Author Year Country	**Population**	**Condition**	**Number of patients**	**FND defined by**	**Costing method Source of cost data Currency**	**Costs Included**	**Intervention**	**Cost per patient before intervention**	**Cost per patient after intervention**	**% change from pre-to-post***

Nielsen et. al [36] 2017 United Kingdom	New patients attending an outpatient neurology clinic specialising in movement disorders and FMS. Symptoms > 6 months causing impairment	FMD	29 in intervention, 25 in control	Fahn-Williams criteria	Bottom up EQ-5D-5L Great British Pound Sterling	QALY (EQ-5D-5L utility score)	Physiotherapy	0.55	0.64	Mean QALYs 0.34 (95% CI 0.31 to 0.37)** (cost per QALY = GBP £12,087
							Standard Medical Care	0.4	0.44	Mean QALYs 0.26 (95% CI 0.22 to 0.30)**
Reuber et al [37] 2007 United Kingdom	New patients referred to outpatient psychotherapy with a specialized service within the neurology departments of the Royal Hallamshire Hospital and the Barnsley District General Hospital between October 2003 and May 2006	FND	63	Consultant diagnosis	SF-6D Bottom up Great British Pound Sterling	QALY (SF-6D score)	Brief psychodynamic interpersonal therapy adapted for functional symptoms	0.53	0.57	. Mean QALYs 0.04** (cost per QALY = GBP £5328)**

Table 1*: Economic characteristics - Studies which assessed costs before and after an intervention (including diagnosis)*

** percentage change refers to the increase/decrease in costs from the period before the intervention to the period after the intervention*

*** Figures refer to mean quality of life measures before and after intervention, and derived QALYs per patient added by the intervention (change pre-to-post), CBT = cognitive behavioural therapy, Tx = treatment, FS = functional seizures, vEEG = video EEG, QALY = quality adjusted life year, FND = functional neurological disorder, FMD = functional movement disorder, ACT = acceptance and commitment therapy, ISTDP = intensive short term dynamic psychotherapy.*

Author Year Country	Population	Condition	Number of patients	FND defined by	Costing method Source of cost data Currency	Costs Included	Comparator	Overall cost	Overall cost per patient	Cost of comparator per patient	FND : comparator cost ratio

Stephen et. al [24] 2020 United States of America	Adults: 2008 to 2017 discharge data from the National Inpatient Sample Children: 2003, - 2016 discharge data from the Kids' Inpatient Database (KID) ED: 2008 to 2017 ED visits from Nationwide Emergency Department Sample (NEDS)	FND	Admissions: 22,895 adult Admissions: 1,264 paediatric ED visits: 36,359 adult, 3800 paediatric	ICD 10 and ICD 9	Top Down NIS [National (Nationwide) Inpatient Sample] KID (Kids' Inpatient Database) NEDS (The Nationwide Emergency Department Sample) US Dollars	Billed services but not professional (physician) fees Expense of the ED or admission presentation to the hospital but not actual societal health care spending by payers or patients	Anterior horn cell disease **(AHCD),** Demyelanting disease **(DD)**, Refractory epilepsy **(RE)**	1,200,000,000 **annually** **Adult inpatient (2017)** $1066 million; 95%CI, $971-$1160 million) **Paediatric inpatient (2012)** $75 million; 95%CI, $57-$92 million **Emergency Department (2017)** $163 million; 95% CI, $144-$182 million	**Adult inpatient (2017)** Mean (SD: $61,700 (800) **Paediatric inpatient (2012)** Mean (SD): $28400 (2100) Could not calculate	Adult inpatient (2017) - **AHCD:** $75,000 **DD:** $55,100 **RE:** $68,900 **Paediatric inpatient (2012)** **AHCD:** $92200 **DD**: $73100 **RE:** $66100 Emergency Department (2017) **AHCD:** $84 million **DD**: $1310 million **RE**: $134.9: million	**Per patient ratio:** **AHCD**: 0.823 **DD**: 1.12 RE**:** 0.896 **Per patient ratio:** **AHCD**: 0.308 **DD:** .0.39 **RE:** 0.43 **Total Cost ratio:** **AHCD**: 1.94 **DD**: 0.124 RE: 1.21
Luthy et.al [27] 2018 United States of America	Patients identified using Pediatric Health Information System (PHIS), an administrative database of 49 North American children's hospitals	FS	399 FS. 13,241 Epilepsy	ICD 9	Top Down Multiplied hospital charge, adjusted for hospital location, by the relevant cost-to charge ratio 2016 US Dollars	Diagnostic studies: Lumbar puncture, brain, spine, and chest imaging, and laboratory tests, ECG, and echocardiogram Attending physicians, social work, therapists	Epilepsy	N/A	$4724 (95% CI $4413–$5057)	$5326	0.887

Author Year Country	**Population**	**Condition**	**Number of patients**	**FND defined by**	**Costing method Source of cost data Currency**	**Costs Included**	**Comparator**	**Overall cost**	**Overall cost per patient**	**Cost of comparator per patient**	**FND : comparator cost ratio**

Goyal et.al [39] 2015 United States of America	IV-rtPA treated patients who presented to one of 4 primary stroke centres	Conversion disorder	538 total, 17 with FND	Diagnostic consensus among 3 physicians, including 2 vascular neurologists	Bottom up Hospital billing department US Dollars	Direct costs: medications, food, consultations, treatments, devices, supplies, and clinical studies. Indirect costs: Utilities, and labour	TIA	N/A	$7,117	$6714	1.06
Jennum et.al [26] 2019 Denmark	People who received a first diagnosis of PNES between 2011 and 2016	FS	873 FS, 1746 controls.	ICD 10	Top Down Danish National Patient Registry, Danish Ministry of Health, National Health Security database Danish Medicine Agency databases Danish Income Statistics 2016 Danish Krone: Converted to euro	Direct costs: medications, food, consultations, treatments, devices, supplies, and clinical studies. Indirect costs: Utilities, and labour	Age and location matched controls	N/A	**Adults**: €41,114 p/a **Costs to partners**: €20,042 p/a	**Adults**: €9,879 p/a **Costs to partners**: €7,495 p/a	**Adult patients** 4.16 **Partners of FND patients:** 2.67

***Table 2**: Economic characteristics - Studies which compared costs to a control group*

IV-rtPA = intravenous tissue plasminogen activator, p/a = per annum, AHCD = anterior horn cell disease, DD = demyelinating disease, RE = refractory epilepsy

Author / Year / Country	Population	Condition	Number of patients	FND defined by	Costing method /Source of cost data / Currency	Costs included	Overall cost	Overall cost per patient	Estimated cost in US Dollars (PPP)	Estimated cost in 2021 US Dollars

Magee et.al [35] 2014 Ireland	Patients diagnosed with NEAD at Beaumont Hospital	FS	Unclear	Unclear	Bottom Up Department of Finance in Beaumont Hospital Euro	Medical costs: Annual recurring direct medical costs, Single-incident direct medical costs, and costs associated with diagnosis and treatment Indirect costs: loss of income tax and Pay-Related Social Insurance (PRSI), and the costs of social welfare	€19,525,629 to €48,289,190 per annum	€20,995.30	$22,845	$24,115
Tinazzi et. al [30] 2021 Italy	Patients with a definite diagnosis of FMD, referred to the Parkinson's Disease and Movement Disorders Unit of Verona	FMD	40	Gupta and Laing	Bottom Up Italian Ministry of Health for inpatients services Veneto Region Tariff Nomenclator for Specialist Outpatient Services Euro	Costs for specialist visits, diagnostic tests, emergency room (ER) visits, hospital admissions, and rehabilitation services in a period of up to 5 years before diagnosis	Annual direct healthcare cost for undiagnosed patients with FMDs of the Italian population is €34.5 million (22.5 covered by NHS and 11.5 by patients)	€2,302 per patient per year [€1,524 covered by the NHS) € 13,812 per patient (€9,144 incurred to the NHS) until diagnosis	$21433	$21433
Nelson-Sice et.al [29] 2019 United Kingdom	Outpatients at St George's Hospital Neurology and Neuropsychiatry FND clinic	FND	71	Consensus diagnosis	Bottom Up CSRI. EQ5D. "Unit costs of Health and Social Care 2016 Curtis L.". Loss of employment based on national average salaries. Informal care £18/hour Great British Pound Sterling	Direct costs: General Practitioner visits, hospital appointments, investigations (MRI, CT, EEG) and medications. Out-of-pocket costs to the patient. Indirect costs to patient and family/carers	N/A	**Over 6 month period** £2564 direct costs. £2374.64 out-of-pocket. £23,108 lost income over 6 month period. £28,110 **total**	$42080	$43,361.00
Seneviratne et. al [31] 2018 Australia	Patients in Monash Medical Centre, Victoria, Australia who underwent inpatient VEM from May 2009 to June 2014	FS	39	Consensus diagnosis +- vEEG	Bottom up Finance department of the hospital Pharmaceuticals Benefits Scheme of the Department of Health, Australia Australian Dollars	Emergency room visits, inpatient admissions, outpatient visits, interventions, Medical Emergency Team (MET) calls for seizures, medications, and investigations (EEG, VEM, electrocardiogram, radiology, blood tests).	N/A	Median: 26,467.63 Australian dollars until diagnosi$s	$18004	$18,549

***Table 3**: Economic characteristics - Studies which did not use a comparator*

Figure. PRISMA flowchart of study identification