Undiagnosing and untreating

psychogenic non epileptic seizures

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Thesis Overview

Psychogenic nonepileptic seizures (PNES) can be defined as paroxysmal events that resemble epileptic seizures, without being associated with either abnormal electrical activity of the brain or primary physiological disturbances otherwise. It is estimated that about 10% of new presentations seen in an epilepsy clinic, and up to 30% of patients with intractable epilepsy will eventually be diagnosed as having PNES (Benbadis & Hauser, 2000).

Attributing a specific 'cause' to PNES is conceptually and clinically contentious but it seems reasonable to say that they represent a physical expression of psychological distress involving behaviour that the patient finds difficult or impossible to control or disavows as being intentional.

Most patients with PNES are initially thought to have epilepsy and treated with antiepileptic drugs (AED), sometimes for many years. Up to 40% of patients are inappropriately maintained on AEDs after the diagnosis of PNES has been established. As such, rather than being intrinsic to the condition, the widely reported poor outcomes associated with PNES may be substantially confounded by continued inappropriate medical management and iatrogenic harm.

Withdrawing or continuing antiepileptic medication in patients with PNES could have important physical and psychological consequences, which may affect the prognosis of the attack disorder. If this is the case, manipulating medication following the diagnosis of PNES may have a role in the management of this disorder. The work contained in this thesis aims to explore some aspects of the effects that continuing or withdrawing AED has on the course and outcome of PNES.

Following an initial general overview on the subject of PNES (chapter 1), a systematic review of the literature is presented in chapter 2; the conclusion being a lack of good quality and reliable evidence for the effects of AED treatment in patients with PNES and a need for further original research in this area. The rationale and programme of research is presented in chapter 3

Chapter 4 presents the results of a large observational study to establish the feasibility and safety of supervised AED withdrawal in patients with an established diagnosis of PNES. Only 3 of the 78 patients included reported a new type of event requiring the reintroduction of AED, and no serious medical events were reported. The study therefore shows that, with appropriate diagnostic investigations and surveillance during follow-up, withdrawal of AED can be achieved safely in patients with PNES.

A randomised controlled trial presented in chapter 5 aims to evaluate the potential therapeutic effect of AED withdrawal. Of the 25 subjects recruited, 14 were randomised to immediate withdrawal (IW) and 11 to delayed withdrawal (DW). Patients randomised to IW had a significant reduction in the use of emergency treatment for PNES, and a lower proportion was found to be using emergency services. The IW group also had a sustained reduction of attacks throughout the study and by 18 months post-diagnosis 50% were attack free as compared with 27% in the DW group.

The results of this exploratory trial suggested a possible therapeutic effect of AED withdrawal, with a sustained reduction of attacks following the withdrawal of medication, coupled with a significant reduction in health care utilisation and no evidence of any deterioration.

The last original paper presented in chapter 6 investigates the longer term psychosocial outcome of PNES with an observational study of the 25 patients included in the RCT. This study reports a significant improvement in some psychological measures; particularly in illness representations and mood, as well as for some measures of social adjustment.

The evidence presented in these three studies (chapter 4, 5 and 6) suggests that a clear delivery of the diagnosis of PNES, followed by AED withdrawal, is safe and has possible beneficial effects on the clinical and psychosocial outcome of PNES. In particular medication withdrawal in and of itself appears to be a helpful concomitant in the successful removal of an inappropriate label of label of epilepsy, reduces the potential for iatrogenic harm, may help patients to shift towards a more psychologically-based explanation, and is associated with positive psychosocial outcomes.

Finally, chapter 7 gives a summary of the main findings as well as discussing methodological limitations of the current research. The clinical implications of the evidence from this body of work are also discussed, as well as possible avenues for future research in the field.

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Chapter 1:

An overview of psychogenic nonepileptic seizures

1.1. Definition

Psychogenic nonepilepstic seizures (PNES) can be defined as paroxysmal events that resemble or can be mistaken for epilepsy, without being associated with abnormal EEG activity or primary physiological disturbance otherwise.

Different terms have been used to describe this clinical phenomenon, from hysterical seizures or pseudo seizures to, dissociative seizures or nonepileptic attack disorder. Up to 15 other terms have been used (Scull, 1997). Some of these terms are seen as pejorative and unacceptable by patients and have been gradually abandoned (Stone et al, 2003). For the purpose of the paper we will use the term, psychogenic nonepileptic seizures (PNES), which is the term that has been most consistently used in recent papers by the main researchers in the field (Reuber, 2008; Duncan and Oto, 2008; La France et al, 2008).

Although not the specific subject of this thesis the difficulties in finding a universally agreed and acceptable term for this disorder is a good illustration of the wider problems of "identity" of PNES (Kanner, 2003), with ongoing debate on questions as fundamental as whether it is a distinct disorder (Taylor, 2001; Wesseley & White , 2004), what is the underlying mechanism (Tojek et al., 2000; Reuberet et al, 2003a; Goldstein et al., 2004a ; Bowman, 2006), or which specialist should manage these patients in the first place (Harden & Ferrando, 2001; O'Sullivan et al, 2006).

1.2. Epidemiology of PNES and associated harms

To appreciate the impact of PNES, different aspects other than the absolute number have to be considered. It is important to be aware that patients with PNES are as disabled by this condition as patients with epilepsy, are high users of medical services and, as a consequence, at great risk of iatrogenic harm.

Epidemiological studies of PNES are difficult since most patients are initially misdiagnosed as having epilepsy and the eventual diagnosis often depends upon the possibility of PNES being considered in the first place. In one epidemiological study the authors noted an increase of the incidence of PNES

during the course of the study, possibly reflecting an increase level of awareness on the part of physicians (Szaflarski et al, 2000).

Specific epidemiological studies of the incidence and prevalence of PNES are sparse but a reasonable estimate can be gained from data on the misdiagnosis of epilepsy, which remains a significant problem (Chadwick & Smith, 2002). Good quality, community-based epidemiological studies have reported rates of misdiagnosis of epilepsy ranging from 20 to 26% and PNES has been found to be the second most common condition to be mistaken for epilepsy after syncope (Scheepers et al, 1998; Smith et al, 1999; Zaidi et al, 2000)

There are two epidemiological studies on the incidence of PNES. The first, from Iceland, calculated the incidence of PNES as 1.4 per 100.000, with the highest incidence for the 15 to 24 age group. This study also estimated that PNES affects 5% of all patients newly presenting with seizures (Sigurdardottir and Olafsson, 1998). The second study was based in Hamilton County in Ohio and estimated the mean incidence of PNES at around 3.03/100000. This study also reported a higher rate of epilepsy than the Icelandic study, which could explain difference in incidences of PNES between the two studies (Szaflarski et al, 2000).

PNES are particularly prevalent in certain settings. Up to 30% of patients with intractable epilepsy referred to an epilepsy specialist centre for further assessment will eventually be diagnosed as having PNES (as opposed to about 10% of new presentations seen in an epilepsy clinic (Benbadis & Hauser, 2004)). Outwith neurology, PNES are not uncommonly seen in patients subjected to acute stressors including mild head injury (Westbrook, 1998; Hudak, 2003) or after a general anaesthetic (Allen et al, 1992; Lichter et al, 2004; Reuber et al, 2000).

In marked contrast to former series, there is an emerging consensus that the coexistence of epilepsy and PNES is the exception rather than the rule. Recent research has consistently reported figures of around 10% (Martin et al, 1998; Benbadis et al, 2001; McKenzie et al, 2009). Although earlier studies reported a co-morbidity of epilepsy and PNES as high as 50% (DeTimary et al, 2002; Reuber et al, 2003b), these numbers are likely to reflect a combination of highly

selected samples deriving from tertiary referral centres, and the more liberal definition of epilepsy adopted in older work, in particular the practice of diagnosing or assuming epilepsy on the basis of non-specific EEG abnormalities.

Even in cases where co-morbidity is confirmed, the clinical picture is generally of frequent PNES in the context of well controlled epilepsy, with the exception of patients with learning difficulties where there tends to be a higher prevalence of coexisting active epilepsy (Duncan & Oto, 2008).

Clinical and psychosocial outcomes are poor. Iatrogenic factors are probably widespread and are certainly responsible for potentially serious adverse physical in particular in the context of 'pseudostatus' (Howell et al, 1989; Brady, 1997; DeToledo et al, 2005). By analogy with epileptic status, pseudostatus refers to prolonged nonepileptic attacks, which can attract an erroneous diagnosis of epileptic status and inappropriate and aggressive treatment, often in an ITU setting. About 10% of patients with PNES will present in pseudostatus at some point and of patients referred to a neurological unit with refractory status, 25% will turn out to have PNES (Walker et al, 1996). Inappropriate use of intravenous AED, general anaesthesia and intubation, are the most immediate and serious iatrogenic harms in PNES (Cohen et al, 1988; Howell et al, 1989; Pakalnis, 1991; Doretzky et al, 2006), the morbidity and mortality for intubated patients being just as high irrespective of whether the diagnosis is epileptic status or pseudostatus.

AEDs have important unwanted effects which have a negative impact on patient's quality of life (Morrow et al, 2006; Meador et al, 2007) and acute, chronic and cumulative iatrogenic harm results from inappropriate prescription of AEDs (Benbadis, 1999; Bode et al, 2007; Duncan & Oto, 2008). The adverse effect profile differs greatly between AEDs, however all can produce detrimental cognitive side effects (Meador et al, 2007).

Patients with PNES also tend to be treated with multiple rather than single AEDs, at higher dosages and with the newer and more expensive AEDs, all factors with a clear economic implication. There is evidence that patients with PNES report more side effects or allergies as compared with patients with

epilepsy. A significant number have been reported to reach toxic drug levels (Krumholz & Niedermeyer, 1983; Reeves et al, 1998; Hantke et al, 2007).

Many AEDs are teratogenic and the risk increases with polytherapy, a feature of particular importance given that the majority of PNES patients are women of childbearing age on more than one AED (Sigurdardottir et al, 1998; Szaflarski et al, 2000). There is now concerning evidence that children who have been exposed to AED pre-natally have higher rates of developmental delay and that children exposed to Sodium Valproate in utero have a significantly lower IQ when compared with controls. This issue is relevant for patients with PNES with an important number treated with Sodium Valporate as the attack disorder is often mistaken for primary generalized epilepsy (Meador et al, 2009)..

The economic burden of this disorder is undoubtedly relevant and probably substantial but the problems of definition, prevalence and highly selected samples again make precise estimates difficult. Direct medical costs for the average patient with PNES before diagnosis, has been estimated to be between $8000 and $15000 per month (Martin et al, 1989; Binder & Slinsky, 2007). Indirect costs and the impact on social and occupational functioning are harder to estimate but the cost associated with loss of work on its own is estimated as $22000 per patient per year (Binder et al, 2007).

Unfortunately, once established reviewing an erroneous diagnosis of epilepsy is expensive and often involves inpatient stays, repetition of imaging and prolonged EEG (Smith et al, 1999).

1.3. General characteristics of patients with PNES

Patients with the diagnosis of PNES represent a heterogeneous group in terms of the aetiology and the manifestation of the disorder (Leiss et al, 1992; Kalogjera-Sackellares, 1997; Cragar et al, 2005; Baslet et al, 2010), however, some common characteristics have been consistently reported.

A consistently reported finding is the over-representation of women amongst patients with PNES, with most studies reporting figures around 75% (Sigurdardottir et al, 1998; Szaflarski at al, 2000; Gates, 2002; DePaola et al, 2006). The only exceptions to this are rates reported in children under the age

of 12, or in older patients (Wyllie et al, 2002; Duncan et al, 2006). However when compared directly demographic, clinical and psychpathological associations of PNES in males and females are broadly similar apart from the higher number of women reporting sexual abuse (Oto et al., 2005).

The reasons for this gender difference are outwith the remit of this thesis but have been a subject of study, comment by a variety of disciplines with PNES and its various equivalents in various historical and cultural milieu being cited as the exemplary socially constructed disease by workers from many theoretical backgrounds. No clear conclusions are apparent but Showalter comprehensively covers this interesting issue in her book “The Female Malady” (Showalter, 1985).

The age of presentation of PNES is frequently reported as between 20 and 40 years of age. However, it is important to bear in mind that PNES can manifest at any age; for example they are not uncommon in children (Wyllie et al, 2002; Bhatia & Sapra, 2005) and have also been described in older adults (Behrouz et al, 2006; Duncan et al, 2006). A large percentage of children with PNES report psychological stressors related to school or relationships with peers (Ercan et al, 2003; Vincetiis et al, 2006) and a recent study of older patients with PNES found lower reports of abuse, suggesting different aetiologies in different demographic groups (Duncan et al, 2006)

High levels of comorbid psychopathology have also been reported in this group of patients, particularly depression and anxiety (Bowman & Markand, 1996; Kanner et al, 1999; Mokleby, 2002) as well as personality disorders, specifically borderline type (Kalogjera-Sackellares & Sackellares, 1997a; Binzer et al, 2004; Reuber et al, 2004). The important issue of associated psychopathology is discussed in detail later on in this chapter.

In summary, although patients with PNES do not conform to a single stereotype it can be said that younger females with high levels of psychopathology and past history of abuse are over represented amongst this patient group (Moore & Baker, 1997).

1.4. Diagnosis

An accurate clinical diagnosis of PNES following thorough history taking and in particular a direct observation of the attacks by an epilepsy specialist is possible in the great majority of cases. (Roberts, 1998; Reuber & Elger, 2003c). The diagnosis of PNES, however, poses specific challenges, since most patients come with a previous diagnosis of epilepsy, which may have gone unquestioned for many years (Reuber et al, 2002; Bodde et al., 2007; Duncan & Oto, 2008; Kuyk et al, 2008). In most cases, therefore, the diagnostic process not only involves making the positive diagnosis of PNES but also removing the firmly attached label of epilepsy.

Taking into account the above considerations as well as the potential consequences of a misdiagnosis, video EEG confirmation of the clinical diagnosis is frequently deemed necessary (Leiss et al, 1992; Cragar et al, 2005).

As well as epilepsy, PNES must also be distinguished from other paroxysmal events, which are mediated by physiological or psychological causes (Roberts, 1998). There are a number of conditions that can present with sudden changes of behaviour or level of consciousness; syncope being by far the most common but the differential diagnosis is exceptionally wide. This introduction will not expand further on the differential diagnosis of blackouts; however for a clear and comprehensive overview see reviews by Roberts and Benbadis (Roberts, 1998; Benbadis, 2009).

1.4.1. Clinical diagnosis

In terms of the clinical diagnosis the ictal semiology or clinical features of the attacks, although not attracting their former level of attention, are important aspects of the diagnosis. Several studies have investigated this issue and reported a range of clinical features that should alert clinicians to the possibility of PNES. The most common clinical features that distinguish PNES from epileptic attacks are listed in table 1. It is important to recognise however that there is no single semiological feature pathognomonic for PNES, and that no

symptom should be considered in isolation when making the clinical diagnosis of PNES (Leiss et al, 1992).

Table 1.1: Clinical characteristics of PNES.

PNES Characteristics
Gradual onset of attacks (Luther, 1992; Meierkord, 1991; Luther, 1992)
Out of phase movements (Gates, 1985)
Side-to-side head movements (Gates, 1985; Groppel, 1999)
Sustained eye closing (Flugel, 1996; DeToledo, 1996; Sirven & Glosser, 1998)
Undulating motor activity (Leis, 1992)
Attacks longer than 2-5 min (Gates, 1985, Binder & Salinsky, 2007)
Quick recovery (Krumholz 1989; Leiss, 1992; Ettinger, 1999)

As well as the clinical features reported in Table 1, other symptoms less commonly seen in PNES can also assist in the differential diagnosis; swooning attacks (limp, still and unresponsive), purposeful moments, rhythmic pelvic movements, responsiveness, and stuttering or weeping during the attack are all more commonly seen in PNES when compared with epileptic attacks (Luther et al, 1982; Gates et al, 1985; Meierkord et al, 1991; Bergen & Ristanovic, 1993; Walczak et al, 1996; Hoerth et al, 2008).

Conversely, certain clinical features considered typical of epilepsy can aften present in PNES. These include autonomic manifestations like tachycardia, flushing and sweating (Goldstein et al, 2007), incontinence and injury, including tongue biting (Pegero et al, 1995; Stone & Duncan, 2006) and provocation of attacks by specific triggers such as flashing lights (Meierkord et al, 1991). Nocturnal attacks have often been thought to be a feature of epilepsy (Roberts, 1998) but are frequently reported in PNES (Duncan et al, 2004).

As well as behaviour during the attacks, other features of patients' behaviour can provide some clues and alert clinicians to the possibility of PNES. Patients with PNES are more likely to have attacks in medical settings (Benbadis, 2005) and to take age-inappropriate soft toys into hospital (Burneo, 2003). PNES patients also appear to have a particular and distinct way of communicating and talking about their attacks that distinguishes them from patients with epilepsy (Schwabe et al, 2007; Plug, 2009).

As detailed in Table 2 (overleaf) various factors in the history and background of patients can often indicate or support a diagnosis of PNES (Reuber & Elger, 2003c).

Table 1.2: Factors in patient background history that should raise suspicion of PNES (adapted from Reuber & Elger, 2003).

Differential Characteristics	**PNES**	**Epilepsy**
Attacks started before 10 years of age	Rare	Common
Attacks in medical settings	Common	Uncommon
Recurrent “status”	Common	Uncommon
Multiple operations and invasive tests	Common	Uncommon
Other medically unexplained symptoms (pain, fatigue)	Common	Uncommon
History of sexual abuse	Common	Uncommon
Psychiatric treatment	Common	Uncommon

It is important to point out that listing sexual abuse as a common feature of PNES (table 2) is an oversimplification. If at one point in the past it was assumed that sexual abuse was the causal event which resulted in patients developing PNES (Betts & Boden, 1996), it is now more the case thatsexual abuse is understood in the context of, and as perhaps merely a particularly specific marker of; poor attachment, family dysfunction and emotional and physical neglect. As mentioned later in this chapter, it is this neglect that results in the person’s vulnerability and the risk of developing PNES (Bowman & Markand, 2005).

It is also important to point out yet again that some of the features listed in table 2 can also be features in the background of patients with epilepsy; for example, a traumatic (as distinct from specifically sexually traumatic) past does not appear to distinguish between patients with or without epilepsy (Berkhoff et al, 1998; Fleisher, 2002).

1.4.2. Diagnostic tests

Video EEG recording of a typical attack remains the gold standard. This diagnostic technique has high specificity and sensitivity. It consists of simultaneous video and EEG recording of typical attacks (Cragar et al, 2002; Cuthill & Espie, 2005).

Unfortunately, Video EEG recording remains an expensive and scarce resource (Silva et al, 2001) but less time consuming and resource intensive diagnostic techniques have been proposed. Short video EEG is an outpatient test, which uses activation or suggestion techniques including photic stimulation and hyperventilation aiming to induce a typical attack. This test represents a cost-effective, as well as an accurate diagnostic technique for PNES, having a diagnostic yield of 50% to 60 % (Bhatia et al, 1997; Srikumar et al, 2000; McGonigal, 2002a).

The use of provocation techniques that aim to increase the diagnostic yield of video EEG remains controversial (Devinsky & Fisher, 1996a). Some authors consider these methods as unethical particularly when placebo is used (Gates, 2001) but others feel that the use of induction techniques is justified in this area where making an accurate and prompt diagnosis is crucial (Lancman et al, 1994; Wasserman et al, 2003; McGonigal et al, 2002b).

The role of other tests such as post-ictal prolactin blood levels, SPECT scan or personality profiles as assessed with the MMPI are limited as diagnostic tools since none of them has high enough sensitivity or specificity to be used alone. Inter-ictal or routine EEG is also of little help and can in fact be misleading since non specific abnormalities are common in the general population and their misinterpretation has often led to the erroneous diagnosis of epilepsy in the first place (DeTimary, 2002; Chadwick & Smith, 2002; Benbadis & Tatum, 2003).

In summary, many studies have been undertaken to identify specific symptoms or psychological features that can aid the diagnosis of PNES and although no feature is pathognomonic an accurate clinical diagnosis of PNES is possible for the majority of patients. Due to the intrinsic complexities of this group of

patient's however, video EEG confirmation is often required for the definitive diagnosis of PNES.

1.5. Classification of PNES

Several classifications of PNES have been suggested over the years, which variously take as their basis the semiological characteristics of the attacks, personality profiles or an underlying psychosocial mechanism (table 1.3). PNES are classified according to the main psychiatric classification systems ICD-10 (WHO, 1992) and DSM-IV (American Psychiatric Association, 1994) as dissociative disorders or somatoform conversion, respectively.

Table 1.3: Criteria for different classification systems for PNES.

1. Classification according to main psychiatric classification (DSM-IV & ICD-10)
2. Classification based on clinical features of PNES
3. Classification according to personality profiles (as assessed by MMPI)
4. Classification according to underlying mechanism of PNES

PNES classification, on the basis of clinical manifestation, range from simple dichotomous classifications of convulsive versus non-convulsive attacks (Meierkord et al, 1991; Gates, 2002) to more complex distinctions of different aspects of the semiology (Flugel et al, 1996). Some authors have linked certain clinical features with specific aetiologies or outcomes, for example Betts and Boden describe "abreactive attacks" in sexually abused females (Betts & Boden, 1996) and patients with more dramatic 'grand mal'-like attacks have been found to have a poorer prognosis (Selwa et al, 2000; Reuber et al, 2002).

The classification of PNES on the basis of clinical characteristics has limited use and can distract from the main issue of the underlying psychological mechanism. Semiological classifications are more or less based on the classification of epileptic seizure proposed by the International League Against Epilepsy (ILAE) and tend to reduce PNES to a false or 'pseudo' version of 'genuine' seizures, rather than a complex and highly heterogeneous psychologically driven phenomenon in its own right. As Leiss et al remark in

their paper on diagnostic pitfalls ‘this type of classifications may artificially produce a focused patient group when none exists’ (Leiss et al, 1992).

Several authors have also attempted to classify PNES according to personality profiles, mainly with reference to the Minnesota Multiphasic Personality Inventory (MMPI). Although some studies have been able to identify distinct groups (Gumint, 1986; Cragar et al, 2005; Reuber et al., 2004) most studies emphasise the heterogeneity of personality profiles among PNES patients (Kalogjera-Sackellares, 1997a; Cragar et al, 2002).

Finally PNES have also been classified according to the possible underlying mechanism. Most of these classifications include broadly similar categories, which are summarised in table 1.4. With this type of classification in mind LaFrance and Zimmerman have designed a potentially useful semi structured clinical interview to categorise patients with PNES according to the underlying psychopathology (LaFrance & Zimmerman, 2010).

Table 1.4: Classification of PNES according to suspected aetiology.

Misinterpretation of physical symptoms	Alsaadi & Marquez, 2005.
Reinforced behaviour	Ford, 1993; Alsaadi & Marquez, 2005.
Cognitive difficulties	Ford, 1993; Lesser, 2003; Alsaadi & Marquez, 2005; LaFrance, 2008.
Stressors and interpersonal difficulties	Ford, 1993; Lesser, 2003; Bowman & Markand, 1996; Alsaadi & Marquez, 2005.
Personality traits	Lesser, 2003.
History of trauma	Bowman & Markand, 1996; LaFrance, 2008.
Psychiatric pathology	Lesser, 2003; Alsaadi & Markand, 1996; LaFrance, 2008.

In summary many authors have attempted to classify PNES using different criteria. The individual classification systems remain unvalidated and although they contribute towards further understanding and conceptualisation of this complex disorder they serve most to illustrate its heterogeneity.

1.6. Aetiology

Major advances in the recognition and diagnosis of PNES have not translated into an increase of our understanding of the underlying cause of the disorder, or

an effective evidence-based management (Reuber, 2008; Brooks et al, 2007). Part of the problem is that patients represent a heterogeneous group (Baslet et al, 2010) and PNES seem to be a symptom of different underlying causes rather than an illness in itself (LaFrance, 2008).

Diagnosis with reference to the current psychiatric classification systems, DSM-IV and ICD-10, has not been particularly useful with PNES being classified as a dissociative disorder under ICD-10 and a conversion disorder under DSM-IV, let alone the fact that many patients also fulfill the criteria for mood and anxiety disorders, PTSD, episodic dyscontrol or, in a minority, factitious disorder (Alper et al, 1995; Bowman, 2001; Fiszman et al, 2004).

Dissociation refers to a disturbance in the normally integrated functions of identity, memory and consciousness, and conversion refers to a loss of function presumed to be of psychological origin. The issue of whether PNES are a result of conversion or a symptom of dissociation is a subject of controversy in some circles (Kuyk et al, 1996; Bowman, 1996; Brown & Trimble, 2000; Goldstein et al, 2000; Prueter et al, 2002) whereas yet others consider somatisation as the characteristic process (Alper et al, 1997; Devinsky et al, 1998; Tojek et al, 2000; Reuber et al, 2003a). Some authors have attempted to resolve these polarities, for example Harden argued that PNES are a form of dissociation which involves conversion-like triggers (Harden, 1997) and Bodde et al pointed out that dissociation has to be seen as one mechanism rather than a cause of PNES (Bodde et al, 2009).

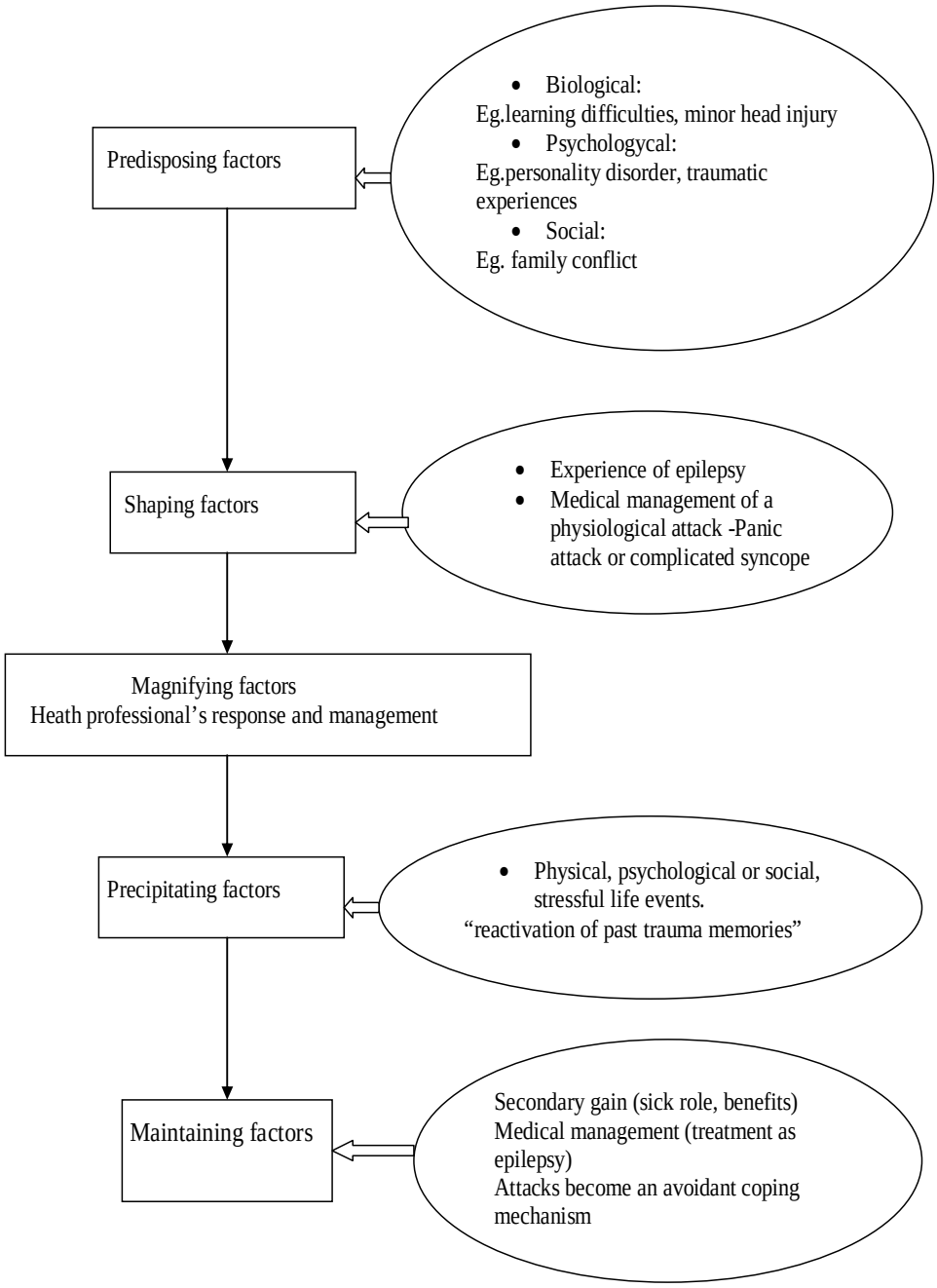
Since there does not seem to be a single mechanism that explains the underlying cause for all patients, the conceptualisation of this disorder using a more general model of predisposing, precipitating and perpetuating factors as often applied to other functional or medically unexplained symptoms has been proposed as more useful for PNES (Stone et al, 2005; Reuber, 2007).

This model, however, has its limitation and some aspects are difficult to fit in or overlap. For example, trauma can be a risk factor or a precipitating factor and depression can predispose or perpetuate the problem. In a recent review Bodde et al attempted to overcome some of these problems by using a modified version which included shaping factors and divided predisposing factors into

those indicating a psychological aetiology or conferring a psychological vulnerability (Bodde et al, 2009).

As regards the model adopted for the purpose of this thesis, and as illustrated in figure 1.1, PNES are conceptualised as arising and existing within a causal matrix with biological, psychological and social aspects.

Figure 1.1: Bio-psycho-social model of PNES



In summary, there are a number of factors in the patients' background that place them at a higher risk of developing PNES in the face of certain stressors, a further set of factors then determine the more or less chronic course of the disorder. Very importantly, the model acknowledges that a substantial influence on the course is independent of the subject, in particular the response of health care providers.

1.6.1. Predisposing factors

Past traumatic experience is one of the most frequently reported associated factors; reports of childhood abuse are high amongst PNES patients and may be predisposing (Alper et al, 1993). A recent review paper for example found rates of reported trauma ranging between 40 -100% and of physical or sexual abuse between 23-77% (Fiszman et al, 2004).

Sexual abuse was considered at one point as one of the main cause of PNES. However, over the last 10 years there has been a shift towards a more nonspecific but possibly more nuanced view of trauma, with sexual abuse conceptualized as a marker of more severe emotional and physical neglect, rather than a specific toxin in itself. Emotional and physical neglect and the associated failure of attachment seem to be a predisposing feature in somatoform disorders in general (Moore & Baker, 1997; Krawetz et al, 2001; Bowman & Markand, 2005; Reuber et al, 2007; Bakvist et al, 2009).

In certain subpopulations of patients with PNES, however, reports of abuse are much lower and other aetiological factors appear more relevant. Patients with learning disabilities for example are likely to develop PNES as a direct response to specific stressors, and for the group of patient that develop PNES later in life, anxiety related to personal health or that of a close relative is often the main trigger (Duncan et al, 2006; Duncan et al, 2008a).

Pathological personality traits are frequently found in patients with PNES, with reports of proportions of patients as high as 75% to 90% fulfilling diagnostic criteria for personality disorder. Borderline personality disorder appears to be the most prominent, although avoidant and dependant personality profiles are

also reported (Reuber et al., 2003a; Galimbierti et al., 2003; Bailles et al., 2004; Binzer et al., 2004).

There is also evidence that certain pre-morbid personality traits and coping styles are associated with PNES. A relationship between PNES and alexithymia (inability to express feelings and emotions) as assessed by the Toronto Alexithymia scale (TAS-20) has been reported (Bewley et al, 2005) and patients with PNES also appear to exhibit disproportionate levels of fear sensitivity (Goldstein et al, 2000).

In terms of coping styles, PNES patients tend to perceive their lives as more stressful when compared with epilepsy patients, and use avoidant and hostile coping mechanisms (Frances et al, 1999).

Associated psychopathology can also been seen as a possible predisposing factor, although at times it is difficult to determine whether psychopathology is part of the primary cause or a factor contributing to the subjects susceptibility to develop PNES. For example, post-traumatic stress disorder (PTSD) is frequently diagnosed in patients with PNES and can be seen as a cause or a predisposing factor, since clearly not all patients suffering with PTSD develop PNES (Bowman and Markand, 1999; Galimberti et al, 2003; Kanner et al, 1999). Rather than proposing a specific causal role for any particular psychiatric diagnosis, psychiatric ‘caseness’ may simply be a marker of a tendency to use maladaptive coping strategies such as dissociation or somatisation, these being likely to significantly predispose patients to develop PNES (Goldstein et al, 2000; Prueter et al, 2002; Reuber et al, 2004; Lawton et al, 2009),

Physical illness and disability can also contribute to someone’s vulnerability to develop PNES. Reports of minor head injury are common among PNES patients (Westbrook, 1998; Pakalnis, 2000). Although not as prevalent as once assumed patients with epilepsy (particularly in the context of learning difficulties) have higher rates of PNES (Lesser et al, 1983; Drake et al, 1992; Moore and Baker, 1997; Barnhill, 2005).

1.6.2. Shaping factors

Many of the factors that appear to predispose patients to develop PNES also apply to other functional or somatic symptoms; however, why an individual patient happens to develop PNES is not clear.

The modelling theory is based on the fact that patient presentations mimic symptoms seen in others (or even themselves) and has been proposed as a possible explanation for a subgroup of patients. Bautista et al. found that up to 60 % of PNES patients reported having witnessed a seizure in the past, and there is also evidence that when compared with patients diagnosed with epilepsy, people with PNES report higher rates of a family history of epilepsy (Bautista et al, 2008; Aldenkamp et al, 1997).

For another group of patients a paroxysmal physiological event, for example syncope, or a panic attack, may be the initial event that shapes the ongoing attacks. When going through the history it is not unusual in this group for the first event to have been a faint or a prolonged panic attack, the level of distress and alarm often being subsequently compounded by involvement of emergency services, the administration of powerful sedatives, and transfer to nigh intensity ‘ medical environments. The subsequent labelling of the attack as ‘epileptic’ and the apparent life saving intervention of powerful medical authority, in concert with preexisting vulnerabilities and experience, can potently influences illness beliefs and PNES can quickly evolve. This process is referred to as pathoplasticity and explains how particular somatic symptoms are shaped according to the medical diagnostic label given to the patient (Barsky & Borus, 1999).

1.6.3. Precipitating factors

Precipitating factors can be divided into stressors or situations that would facilitate the attack disorder to emerge at a particular time, and immediate stimuli or situations that would predictably trigger attacks in patients with established PNES. A variety of factors have been described as immediate triggers for PNES: flashing lights, tiredness or as a direct response to stress (Lancman et al, 1994; Benbadis, 2005).

Stressful or traumatic life events previous to the start of the attack disorder can be identified in the majority of patients (Fleisher et al, 2002; Binzer et al, 2004). A wide variety of events have been reported as possible triggers for PNES including; family conflict, relationship problems, bereavement, abuse, and money and work difficulties, amongst others (Gardner, 1982; Pakalinis, 1991; Moore & Baker, 1997; Bowman & Markland, 1999; Salomon et al, 2003). Bowman clearly distinguished between; immediate, remote and contextual precipitating factors, and concluded that the most common mechanism seems to be "the reactivation of emotions of past trauma by a variety of precipitants" (Bowman & Markland, 1999).

Physical stressors like surgery, pregnancy have also been reported (William & Huff, 1997; Reuber et al, 2000; Lichter et al, 2004; Collard, 2010). Toxic levels of AED have also been linked to the genesis of PNES (Niedermeyer et al, 1970).

The problem with most of this research, however, is that the temporal relationship of the event and the start of PNES are often not clearly defined and remote, ongoing or acute events are often reported together. Another issue is that most of these studies are not controlled or compared to patients with epilepsy, limiting their relevance. As Bowman points out, it is likely that these different triggers have to be been seen in the context of an individual patient's vulnerability and past experiences (Bowman & Markland, 1999; Bowman, 2001).

1.6.4. Perpetuating factors

Having an illness can excuse patients from certain responsibilities as well as entitling them to compensation in the form of financial and practical help. Secondary gain, the notion that behaviour is motivated by explicit material reward as well as implicit, or unacknowledged psychic conflict, is possibly needlessly pejorative and a substantial oversimplification of the plight of patients who get stuck in the sick role. However, receipt of enhanced state benefits could be a powerful disincentive to recovery and has certainly been reported as

a factor for a poor prognosis (Kristensen & Alving, 1992; McKenzie et al, 2009, Sharp et al, 2010).

Relatives' beliefs and their reinforcement of the illness behaviour can also perpetuate the symptoms (Sirven & Glosser, 1998; O'Malley et al, 1999). Family dynamics can also play an important role; families of patients with PNES have been found to be more hostile and less supportive when compared with epilepsy patients (Mokleby et al, 2002; Stanhope, 2003; Lacey et al, 2007).

A potentially preventable perpetuating factor is clinical iatrogenesis, since health care professionals have an important role in magnifying and perpetuating PNES. 'Medicalisation' refers to the exclusive and reductive adoption of a model that emphasizes passivity in the face of an organic process and reliance and dependence upon medical technology. Medicalisation can have a powerful effect on any patient unfortunate enough to attract a diagnosis of epilepsy, erroneous or not, but is of particularly relevance in a group of patients who already have a tendency to interpret their attacks as unpredictable and out of their control and to attribute their symptoms to physical causes in the first place (Stone et al, 2004; Goldstein & Mellars, 2006).

Patients often report feelings of anger and uncertainty following a diagnosis of PNES (Green et al, 2004; Carton et al, 2007). These problems are considerably compounded by ambiguous management (such as leaving patients on AED following the diagnosis), and repetition of speculative, redundant or unnecessary medical tests with low diagnostic yield in a fruitless attempt to bring about consensus (Martin et al, 1998).

In summary, patient illness perceptions as well as external factors that can reinforce their behaviour can influence the course of PNES once established.

1.7. Management and prognosis

Our knowledge of the best management strategies for PNES remains limited and although several psychotherapeutic interventions have been described there is little evidence for any one in particular (Brooks et al, 2007). This is possibly a reflection of the fact that PNES is not a disease entity but a symptom

of a variety of underlying psychological and psychiatric problems requiring a range of treatments (Leiss et al, 1992; Kalogjera-Sackellares, 1997b; Cragar et al, 2005; Baslet et al, 2010).

However, while acknowledging this therapeutic uncertainty the initial management of PNES in terms of assessment, diagnosis, communication and the withdrawal of iatrogenic harm is a generic intervention independent of associated psychopathology (Shen et al, 1990; Farias et al, 2003; Thompson et al, 2005; Howlet et al, 2007; Hall-Patch et al, 2010). Effective communication is particularly important in a group of patients who are often hostile and frequently report feeling confused and angry after the diagnosis (Green et al, 2004; Thompson et al, 2009).

The clinician's familiarity and confidence with the diagnosis in this context is paramount since patients have generally had many contradictory explanations for their symptoms and usually challenge the initial diagnosis (Harden et al, 2003). A better outcome has been associated with patients' belief in and acceptance of the diagnosis of PNES (Ettinger et al, 1999b).

Communicating the diagnosis in a clear and supportive manner is for some patients the only intervention required, and even when attacks persist there is evidence that following a confident diagnosis of PNES there is a significant reduction of health care utilisation by the patients (Buchanan & Snars, 1993; Martin et al, 1998; Kanner et al, 1999; Farias et al, 2003).

Standardised ways to communicate the diagnosis have been proposed and a recent study from Hall-Patch et al. assessed the acceptability of a comprehensive communication protocol supported with written information (Hall-Patch et al, 2010). Subsequent work has this protocol to be an acceptable and effective component of efforts to communicate a psychological explanation for PNES (Shen et al, 1990; Betts & Boden, 1992).

As most patients with PNES are treated with AED, withdrawing medication is the next logical step following the delivery of the diagnosis. Up to 40% of patients, however, are left on medication at this point (Benbadis, 1999; Reuber & Elger, 2003c; O'Sullivan et al, 2007; Hall-Patch et al, 2010). This not only

places them at an increased risk of iatrogenic harm but also contributes to feelings of confusion following the diagnosis (Green et al, 2004).

There is some evidence for the effectiveness of psychotropic medication in medically unexplained symptoms. However in the context of PNES, although antidepressants, particularly SSRIs, have been recommended and other psychotropic medication has been used, the evidence of benefit is anecdotal and use of psychotropic medication in PNES is indicated mostly on the basis of co-morbid psychopathology (Alper et al, 1997; Reuber & Elger, 2003c; LaFrance & Devinsky, 2004).

When the diagnosis of PNES is established most patients are referred on for further psychological treatment (LaFrance et al, 2008) although, as already mentioned, there is little evidence for any particular psychotherapeutic management strategy although a wide variety of psychotherapeutic interventions have been proposed. Behavioural approaches, psychodynamic based interventions, hypnosis, psycho education andr family therapy amongst others have been all described in small case series (Griffith et al, 1995; Kuyk et al, 1995; Aboukasm et al, 1998; Prigatano et al, 2002; Zaroff et al, 2004; Kallogjera-Sackellares, 2004; for reviews see Reuber, 2003; LaFrance & Devinsky, 2004; Barry et al, 2008; Bodde et al, 2009).

Of all the different interventions, Cognitive Behaviour Therapy (CBT) is the one that has been more systematically evaluated. LaFance et al tested the effects of their CBT protocol specifically designed for patients with PNES in an open label study and reported significant improvement in a range of clinical and psychological factors (LaFrance, 2009). Following a pilot study, Goldstein et al. published one of the only RCTs on treatment of PNES, they randomised 66 patients to 12 sessions of weekly CBT or standard medical care and concluded that CBT is more effective in reducing attack frequency, however they were unable to detect changes in most of their psychosocial outcomes (Goldstein et al, 2004; Goldstein et al, 2010).

The only Cochrane review on the treatment of PNES, managed to identify three small randomised controlled trials, two comparing the effects of hypnotherapy

and a third one comparing paradoxical intention treatment to regular Diazepam No overall conclusion could be reached (Brooks et al, 2007).

Another recent review found some evidence of better outcomes for inpatient multidisciplinary treatment strategies (LaFrance, 2007; Kuyk et al, 2008), but other authors have pointed out the importance of treating patients in their own environment as more relevant to addressing precipitating or perpetuating stressors and triggers for PNES (Betts & Boden, 1992; Buchanan & Snars, 1993).

Although intensive interventions appear to result in attack freedom in a high proportion of patients in the short-term, gains tend not to be maintained and the majority of patients relapsed over subsequent follow-up (Farias et al 2003; O'Sullivan et al, 2006) according with the fairly general finding that whatever the treatment modality employed only a third to a half of patients are reported to be attack free within two years of the diagnosis (Iriarte et al, 2003; Reuber, 2003; DePaola et al, 2006).

The usefulness of much of the literature is somewhat diluted by doubts about the validity of attack freedom or reduction as an outcome. There is evidence that reduction or cessation of attacks, although useful as an objective clinical outcome measure, may not correlate with psychosocial recovery and the importance of including comprehensive and relevant psychosocial measures of outcome has been stressed by a number of authors (Quigg et al, 2002; Reuber et al, 2003b; LaFrance et al, 2008).

As shown in table 1.5 (overleaf), several studies have reported prognostic factors for the outcome in PNES. Methodological problems are generally apparent (Ettinger et al, 1999b) and all that can be said with confidence is that measures reflecting good pre-morbid social adjustment and functioning, as well as lower levels of psychopathology, correlate with a better outcome.

Table 1.5: Studies reporting prognostic factors for PNES outcome.

	Study	No. subjects	Attack free	Good prognosis for NES	Poor prognosis for NES
1	Aboukasm et al 1998	61	53%	Therapy +feedback by epilepsy specialist	
2	Arain et al 2007	48	35%	Higher education Mostionless spells Accompanied to clinic	
3	Drake et al 1992	20	NA~	Patients with conversion improved when AED withdrawn	
4	Ettinger et al 1999	56	51.80%	Believing the diagnosis In employment Perceived good health	
5	Kanner et al 1999	45	29%		Personality disorder Recurrent depression
6	Lancman et al 1993	96	25.40%		None of the factors tested was associated with poor outcome
7	Kristensen et al 1992	28	45%		Receiving state benefits
8	Meierkord et al 1991	110	40%	Female Independent life Formal psychotherapy No coexisting epilepsy	
9	O'Sullivan 2007	38	16%		Resistant to psychotherapy Impaired social function
10	Selwa 2000	57	40%	Less dramatic attacks Shorter duration of the disorder	
11	McKenzie et al 2009	187	38%	Male gender	History of anxiety & depression Receiving state benefits
12	Silva et al 2001	17	38%	Independent life style Accepting diagnosis	
13	McDade & Brown 1992	18	44.40%		Low IQ Violent behavior
14	Walczak 1995	51	35%	Shorter duration of NES No psychiatric disorders	

1.8. Conclusion

This introduction provides an overview of the main aspects of PNES, and although informed as comprehensively as possible by published evidence, it must be made clear that this is not a systematic review and reflects to some extent the views of the author. The main objective of this chapter was to set the scene for the original research of the thesis.

PNES are not uncommon and represent a significance problem to a variety of clinicians. Compared with our ability to diagnose PNES, our understanding of this disorder, in terms of its underlying mechanisms, and particularly with reference to treatment, remains limited. Beyond diagnosis there is very little evidence for any particular therapeutic intervention and as Reuber discusses in his review we are left with more answers than questions (Reuber, 2008).

One of the major issues in patients with PNES is the potential for iatrogenic harm, largely associated with AED. In this area many questions remain unanswered; Is withdrawing the medication necessary in all cases? Is it harmful to leave or withdraw patients' AED? Or is AED withdrawal an intervention in its own right? A panel of experts intending to design a treatment trial for PNES also discussed all these questions (La France, 2006). The current thesis intends to answer these questions with a combination of observational studies and an RCT on the effects of AED withdrawal.

Chapter 2:

Does discontinuation of antiepileptic drugs affect the outcome of nonepileptic seizures? A systematic review of the literature.

2.1. Abstract

Background: Psychogenic nonepileptic seizures (PNES) are psychologically mediated attacks that resemble and are often mistaken for epilepsy. Most patients are initially treated with antiepileptic drugs (AED) and a significant proportion continue to receive this medication after the diagnosis of PNES has been confirmed. Continuing antiepileptic medication in patients with PNES may have important physical and psychological consequences and may affect the prognosis of this disorder.

Objectives: To review the current literature for any evidence of an effect of continuation of AED treatment on the outcome of PNES.

Methods: Search strategy; Ovid MEDLINE (to Aug 2009), EMBASE (Oct 2009), PsycINFO (Oct 2009), Cochrane database of systematic reviews. According to our selection criteria; English language studies of adults with PNES containing data on the impact of AED on the prognosis, were included.

Results: The search identified 3 observational studies, two of which reported the continuation of AED as having a negative effect on the outcome and a third no effect. All of the selected studies had important methodological limitations.

Conclusions: Because of the limited quality of the selected studies it was not possible to conclude that there is a correlation between taking AED and an adverse outcome. A randomised controlled trial would be the only way to establish if withdrawing AED at diagnosis contributes to a better outcome in patients with PNES.

2.2. Introduction

Psychogenic non-epileptic seizures (PNES) may be defined as paroxysmal events that resemble and/or are treated as epileptic seizures without being associated with any measurable alteration in the electrical activity of the brain and are thought to have a psychological underlying cause. Outcome is often reported as poor but there is little evidence-based knowledge on how best to treat this disorder.

Most patients with PNES are diagnosed with epilepsy and therefore treated with AED, sometimes for many years (Benbadis, 1999; Bode et al, 2007; Duncan & Oto, 2008). As described in chapter 1 (page16), the effect of inappropriate prescription in this population has been increasingly recognized, investigated and reported. Specific maladaptive patterns of medication taking, possible unrecognised psychotropic effects of AED, and the impact that taking AED may have on the patient's understanding of their disorder have been described or proposed (Reeves et al, 1998; Hantke et al, 2007; LaFrance et al, 2006; Carton et al, 2003) .

The role of AED in the diagnosis of PNES has been frequently reported in the literature. For example, a lack of response to AED and higher reports of side effects support the diagnosis of PNES as opposed to epilepsy (Bowman & Coons, 2000; Hantke et al, 2007). There is also some anecdotal evidence to suggest that AED can be implicated in the genesis of PNES and possible mechanisms have been proposed; from forced normalisation, AED toxicity or the consequence of an idiosyncratic side effect (Trimble, 1996; Neidermeyer et al, 1970; Weaver, 2004).

Although tapering AED after diagnosis is recommended as being part of treatment as usual for PNES (LaFrance, 2008) up to 40% of patients with PNES continue to be prescribed AED after the diagnosis is established. This in itself may adversely influence the outcome (Reuber et al, 2003a; O'Sullivan et al, 2007).

Withdrawing or continuing antiepileptic medication in patients with PNES can therefore have important physical and psychological consequences, which may affect the prognosis of the attack disorder. If this is the case manipulating medication following the diagnosis of PNES could have a role in the management of the disorder.

Our hypothesis is that withdrawing medication after the diagnosis of PNES is a congruent and important therapeutic step in management, with positive effects on the outcome.

The purpose of this paper is to review the current literature for evidence about the effect of taking AED on the outcome of PNES.

2.3. Methodology

Research question:

Does discontinuation of antiepileptic drugs influence the outcome of nonepileptic seizures?

Search strategy:

The electronic search included the following databases Ovid MEDLINE (to Aug 2009), EMBASE (Oct 2009), PsycINFO (Oct 2009), Cochrane database of systematic reviews.

The search terms included [Pseudoseizure$], [Pseudoepilepsy] or [Hysteroepilepsy] [Nonepileptic], [dissociative], [hysterical], [conversion] or [psychogenic] combined with [seizure] or [attack] combined or not with [disorder].

The above search was linked to the terms [Antiepileptic drug$], [Antiepileptic medication] and [Anticonvulsant$].

The references of several review articles identified through the search were also examined in order to identify further relevant studies and improve the sensitivity of our search.

2.4. Data collection and analysis

Inclusion criteria:

- Papers where the study population had the diagnosis of PNES
- Studies including data on AED, particularly on its effects on course and prognosis of PNES
- Studies written in English
- Studies including adult populations only

Assessment of the quality of the studies

To our knowledge there are no rating scales to assess the quality of outcome studies on PNES. We have therefore designed a scale based on a suggested checklist of items that should be included in reports of observational studies by the STROBE statement and suggestions from a Consensus statement on the characteristics of a clinical trial on outcome measures for PNES (La France et al, 2006).

A study of PNES ideally will include only patients with video EEG confirmation of the diagnosis and exclude patients with coexisting epilepsy. The outcome measures should include psychosocial outcomes with a follow up time of at least 12 months to be sensitive to changes of all outcomes. In terms of sample size we considered a sample that at least would be able to detect (or exclude) a large effect.

Our 14 point scale (see appendix A) combined generic methodological points as well as specific issues for PNES (LaFrance et al, 2006).

The checklist from the STROBE statement (appendix B) was also used as a template for the methodological review of the individual papers.

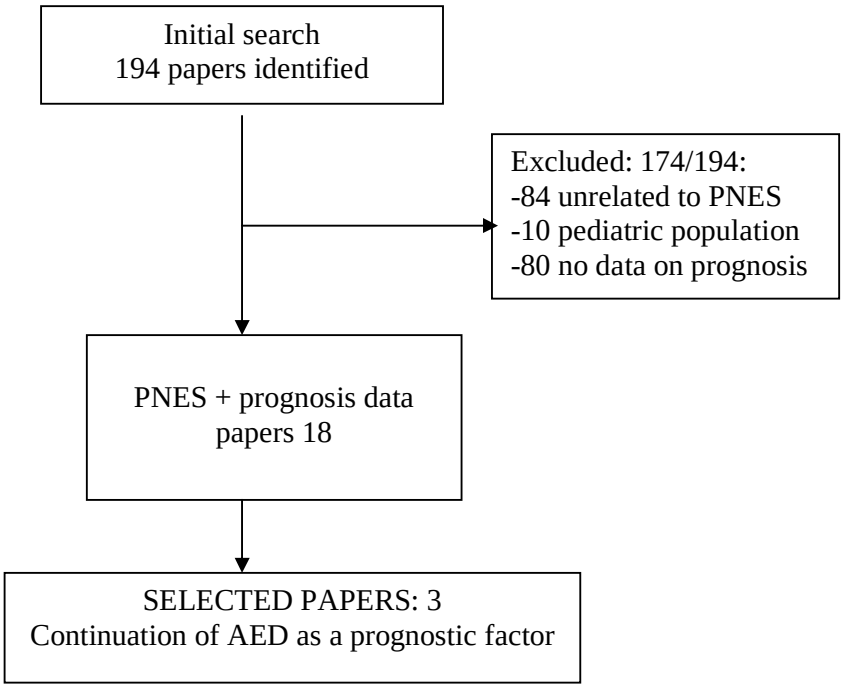
2.4.1. Selection of studies

The search yielded 194 citations in total. The author inspected all the citations identified from the search and selected 20 relevant studies of patients with PNES that reported prognostic factors. These papers were fully inspected for inclusion criteria by the author and a research assistant independently and in case of disagreement, a decision was reached by discussion. Of the 20 papers, two were reviews and therefore not included and 14 had no data on continuation of AED as a prognostic factor.

No randomised controlled trials were identified. Of the studies containing outcome data we found four observational studies that had data correlating outcome of PNES with taking AED's. Two of these studies were based on the same sample and methodology therefore we have reported them together.

For the break down of selected papers see the flow chart below.

Figure 2.1: Flow-chart of paper selection for review.



2.5. Results

2.5.1. Summary of the rejected studies

Of the relevant studies, 14/18 were not included since they contained no data on continuation of AED as a prognostic factor (see table 2.1).

Table 2.1: Description of rejected studies.

	No. Subjects	AED At diagnosis	AED At follow up	Attack Free	Good Prognosis for NES	Poor Prognosis for NES
Aboukasm et al 1998	61	63.90%	22.90%	53%	Therapy +feedback by epilepsy specialist	
Arain et al 2007	48	85%	100%	35%	Higher education Mostionless spells Accompanied to clinic	
Drake et al 1992	20	100%	NR	NA~	Patients with conversion improved when AED withdrawn	
Ettinger et al 1999	56	48.20%	32.40%	51.80%	Believing the diagnosis In employment Perceived good health	
Kanner et al 1999	45	NR	NR	29%		Personality disorder Recurrent depression Chronic abuse
Lancman et al 1993	93	53.80%	NR	25.40%		None of the factors tested was associated with poor outcome
Kristensen et al 1992	28	86%	62.50%	45%		Receiving state benefits
Meierkord et al 1991	110	NR (majority)	NR	40%	Female Independent life Formal psychotherapy No coexisting epilepsy	
O'Sullivan 2007	38	1.5 +/-1.4 (mean number)	35%	16%		Resistant to psychotherapy Impaired social function
McKenzie et al 2009	187	52%	13.2%*	38%	Male gender	History of anxiety & depression Receiving state benefits
Silva et al 2001	17	72.70%	36.30%	38%	Independent life style Accepting diagnosis	
McDade & Brown 1992	18	1.88 (mean number)	NR*	44.40%		Low IQ Violent behavior
Walczak 1995	51	38/51(74.5%)	53%	35%	Shorter duration of NES No psychiatric disorders	
Selwa et al 2000	57	NR	32%	40%	Shorter duration of the disorder, Less dramatic attacks	

*Intent to withdraw AED reported
NR = not reported

All these studies were observational and from tertiary referral centres. As shown in table 2.1, samples size ranged from 18 to 187 subjects and the follow up times varied from days to years, not only between studies but also within subjects as individual studies report a wide range of follow-up lengths amongst patients.

As is detailed in table 2.1, in terms of prognosis, most papers report measures reflecting independent life style and social adjustment of the subjects as positive prognostic factors. On the other hand, receiving state benefits, the chronicity of the disorder and high level of psychopathology are correlated with poor prognosis, with the exception of the two larger studies that found no relationship with chronicity and attack freedom.

In terms of the number of patients exposed to AED, most studies report high percentage at diagnosis, however not all studies report the number of patients continuing on AED at follow up. Only two studies make reference to the number of patients who are attack free and not on AED. Buchanan et al. found that the less chronic group, with a high percentage of attack free patients at follow up, are less likely to be on AED; and Drake reports an improvement of all patients with conversion disorder (n=10) following the withdrawal of medication.

In the study by Arain et al, medication was withdrawn in all patients following the explanation of the diagnosis. At follow up (time was not specified), 35% of patients were attack free.

The study by O'Sullivan et al also considered the possibility of different outcomes between subjects taking AED with, or without, mood stabilising effects, and found no significant difference in a range of psychosocial outcome measures. The same authors also found that males were more likely to be on AED before and after the diagnosis.

2.5.2. Selected studies: Description of selected studies

Two of the 4 selected papers, presented different outcome data from the same study and are therefore described together (see table 2.2 for description of studies and table 2.3 for assessment of quality criteria).

Table 2.2: Description of selected studies.

	Sample							Follow up						
	Design	Population	*N*	Epilepsy included	% Video EEG diagnosis	Response rate	Management	Folllow-up: Years (sd)	% Attack free	AED at diagnosis	% ongoing AED	Continuation of AED effect on outcome	Predictors of good outcome	Predictors of poor outcome
Carton et al 2003	Postal questionnaire Cohort	Specialist centre	84	No	NR	84/115 (73%)	No Treatment Protocol	4.7(NR)*	28%	NR	32%	Negative	Employed, reaction to diagnosis (relief of not having epilepsy)	Continuation of AED, reaction to diagnosis (confusion or anger)
Bode et al 2007	Phone questionnaire cohort	Specialist centre	21	No	100%	22/28 (78.5%)	No Treatment Protocol	4.7(1.3)	47.6%*	13.50%	NR	No effect	Higer education, younger onset of NES, less dramatic attacks	Higer scores on dissociation, higher scores on personality traits (inhibitedness, emotional dysregulation & impulsivity)
Reuber et al 2003	Postal questionnaire cohort	Specialist centre	164	Yes	55.40%	164/329 (49.8%)	No Treatment Protocol	4.1 (3)	28.60%	75%	40.70%	Negative	-	Associated psychopathology, high scores of self-avoudant behaviour

**4 to 6 years NR, not reported*

2.5.3. Paper 1- Non-epileptic seizures: patients' understanding and reaction to the diagnosis and impact on outcome. (Carton, S., Thompson, P.J. & Duncan, J.S)

This was an open non randomised postal questionnaire study of 84 patients with confirmed PNES without coexisting epilepsy, seen at an epilepsy specialist centre and reviewed 6 months to 7 years following the diagnosis.

Patients answered a semi structured interview over the phone and demographic information was sourced from medical notes. A short questionnaire was also sent to their GP's.

The main outcome of the study was attack freedom, and the prognostic factors considered in the paper related to the understanding of, and reaction to, the diagnosis of PNES by the patient. The authors also considered prognostic factors previously reported in the literature, which they grouped into precipitating factors, negative impact of PNES on daily life, and psychological follow up.

The sample was drawn from 115 patients diagnosed with PNES only during an inpatient assessment at a tertiary referral centre over a period of 8 years.

The follow up period ranged between 6 month to 7 years and the length of the disorder ranged between 1 month to 41 years (no data on standard deviation were given).

By the end of the study, 28% of patients were seizure free and a further 48% reported a >50% reduction of attacks, almost a third of patients (32%) remained on AED. Only a third of the patients had some understanding of the diagnosis of PNES and the most common reaction to diagnosis was confusion.

In terms of prognostic factors patients who; continued the AED ($p<0.0001$), or had described confusion ($p<0.001$), or anger ($p<0.002$) at the diagnosis of PNES, were more likely to continue to have attacks. Conversely, patients who reported relief following the diagnosis of PNES ($p<0.0001$), or were employed ($p< 0.009$), were more likely to be attack free.

Methodological quality

The introduction of the paper contained good background information and clearly stated the objectives of the study, however did not specify the main hypothesis.

For the study design a combination of qualitative and quantitative methods was used and this was clearly described. The settings and data collection were also well described.

The sample came from the inpatient population of a tertiary referral centre which makes it comparable to most of the published studies on PNES; however, the population may not be representative of patients selected from the community, or a general practice setting.

It is unclear how the 115 patients were selected; whether they were consecutive or what percentage of the total number of patients assessed they represented.

The eligibility criteria of the participants appeared clear, patients had an unequivocal diagnosis of PNES; however, the percentage of patients with video EEG confirmation, which was one of our quality criteria, as shown in table 2.3, was not reported.

Another point in our quality criteria scale was the exclusion of patients with epilepsy, and although that was the case for this study, the authors did not define the criteria for the diagnosis of epilepsy.

The outcome variables were clearly described and steps were taken to ensure precise and unbiased measurement. This was achieved by combining self report with GP data and by assessing inter-rater reliability for the qualitative data. The prognostic factors were also fully defined and appropriate to the objectives of the study.

The sample was also well described and the characteristics comparable to samples of other similar studies. The rest of the results were also clearly

presented and although the outcome data is quantitative, some appropriate qualitative data is presented.

Simple and appropriate statistical tests were used; however, multiple testing, particularly considering the small sample, was an issue.

One of the main drawbacks of the paper is the lack of definition or standardisation of the intervention. It is not clear whether all patients had the same type of assessment, or how and by whom the diagnosis was communicated. Considering that the main objective of the study was to assess the reaction and impact of diagnosis, the above points are particularly relevant since there is evidence that the initial intervention of delivering the diagnosis is very important and can influence the prognosis (Ettinger et al, 1999b).

Another important factor that can affect prognosis, and was not accounted for in this paper, was the chronicity of the disorder, which varied greatly between patients from months to years.

The type of psychological intervention that patients received was not clearly described, however it appears that there was not a standard approach for all subjects and the length of the intervention also varied widely.

The above points were potential sources of bias particularly in this study were the outcome of interest was the understanding of, and reaction to, the diagnosis.

Another important point when considering the quality of the study is the homogeneity of the subjects in terms of follow-up times. The length of follow up varied widely from 6 months, which would be considered short term, to 7 years, which is obviously long term. There is evidence that short term outcome is more favourable and this is also not taken into consideration in the present study.

In terms of the rating of the methodological quality, this paper scored the highest (table 2.3); however, as with most studies in the field, important interventions are not standardised and although that was only one of our points

in our quality checklist, this represents a particularly important point when trying to interpret the results.

Table 2.3: Quality criteria for selected studies.

	Carton et al	Reuber et al	Bodde et al
Representative sample			
Explicit inclusion criteria	X	X	X
Coexisting epilepsy excluded	X		X
Avoid patient selection bias	X	X	X
Video EEG diagnosis			X
Similar disease length			
Sample size > 75	X	X	
Sufficient length of follow up		X	X
Similar length of follow up			
Drop out rate <40%	X		X
Standardized intervention			
Valid outcome measures	X	X	
Clearly stated outcome measures	X	X	
Objective measure of outcome	X	X	X
Final score	**8/14(57%)**	**7/14(50%)**	**7/14(50%)**

2.5.4. Paper 2-, Factors involved in the long-term prognosis of psychogenic nonepileptic seizures. (Bodde,N.M.G., Janssen,A.M.A.J., Theuns, C., Vanhoutvin, J.F.G., Boon, P.A.J.M. and Aldenkamp, A.P).

This was a prospective observational study of 22 patients with confirmed PNES and no associated epilepsy, assessed at baseline and 4 to 6 years post-diagnosis with an average of 4.7 years post diagnosis (SD 1.3).

The aim of the study was to investigate factors involved in the long-term prognosis of PNES. Improvement was defined as any reduction in attacks from baseline.

As outcome measures, the authors included self reported attack frequency, and psychological rating scales including the Symptom Check List, The Dissociative Questionnaire and the MMPI.

Out of the 22 patients included in the study 86.4% were female; the average age was 30.4 years (range 15- 49); and there was an average diagnostic delay of 7.2 years. At baseline only 13.5% of patients were on AED and 41% reported daily attacks. At follow up, 7/22 (31.8%) of the sample had been attack free for at least one year.

No relationship was found between attack reduction and any of the demographic or clinical data at baseline, including use of AED's.

Linear regression, used to analyse possible psychological predicting factors, showed that higher psychopathology and self-avoidant behaviour predicted poor improvement. No association was found between any specific personality profile and improvement.

Methodological quality

In the introduction of the paper the reasoning behind the study was explained together with clear background information; however, the specific objectives were not clearly stated and there was no hypothesis defined.

The study design was not fully described and the 'settings' were unclear, particularly information on how and by whom the patients were assessed, and on how the data was collected. The eligibility criteria for the subjects were clear with precisely described diagnostic standards and a good description of the instruments used to measure outcomes.

The objective of the study was to investigate possible associations between attack reduction and a series of measures. The way the results were presented, however, was confusing: it was not clear which were the important or most relevant findings and some of the outcome data was reported for the whole group rather than comparing the good and poor outcome subjects.

For our quality checklist the sample had to be greater than 75 and the sample of this study was much smaller (n=22). The small sample size was particularly problematic considering the amounts of statistical tests that were performed.

From the point of view of association between AED and outcome, the fact that the number of patients on AED was very small, and the majority of patients had a reduction of attack frequency, a negative result should be viewed with caution.

As shown in table 2.3, the lack of valid outcome measures was an issue in terms of the quality of the study. The author's definition of a good outcome included any reduction of attacks from baseline, which cannot be considered a good outcome in itself since most published studies show a reduction of attacks following diagnosis, regardless of intervention (Bodde et al, 2007). We can argue, therefore, that some of these patients did not in fact have a clinically meaningful change, and that a minimum reduction of 50% of attacks, as used in many studies, would have been more relevant as an outcome measure of improvement.

Another measure with questionable validity is the use of the MMPI to assess changes in psychological symptoms. The MMPI is a personality inventory, and since personality, by definition, is a set of reasonably stable traits, a different scale designed to assess changes particularly in such a short time-frame would have been more appropriate.

The discussion of this paper suggests that the good outcome of the study in terms of attack freedom may have been a result of the impact of the diagnostic process and delivery. The problem is that there is no evidence in the paper that there was any standardised or agreed procedure for delivering the diagnosis and therefore it does not appear that all subjects had the same intervention. From this point of view an association cannot be made.

The main weaknesses of this paper, in terms of methodological quality, were the small sample size and the fact that the main outcome measure was not valid to assess improvement of PNES.

2.5.5. Paper 3(a)- Outcome in psychogenic nonepileptic seizures: 1 to 10-year follow-up in 164 patients. (Reuber M., Pukrop R., Bauer J., Helmstaedter C., Tessendorf N., Elgar C.E.)

This study was a postal questionnaire on the long term outcome of PNES with or without epilepsy. Of the 329 patients identified from a tertiary referral centre database, 164(49.8%) responded.

The aim of the study was to identify clinical and psychological factors that may predict the outcome of patients with PNES. Outcome measures included; attack freedom, social adjustment, personality traits and level of psychopathology. Patients were grouped into good, intermediate or poor outcome according to attack freedom and level of social functioning.

Of the 164 responders, 130 (79.3%) were women and only a minority had been in higher education. The mean age was 38.6 (sd: 14) and the mean duration of follow up was 4.1 (sd: 3) years.

Following the diagnosis, patients were managed by the local referring team. A high number were treated as inpatients; 68(41.5%) on a psychiatric ward and 134(81.9 %) in a neurology ward.

At follow up 43.9% of patients had a “poor” outcome and only 16.2% were considered to have a good global outcome which implied being attack free and working. The majority of subjects, 116 (71.2%), continued to have attacks and 66 (40.5%) were still dependant.

In terms of factors predicting outcome; younger age, higher educational attainment, less dramatic attacks, few somatoform complaints and low dissociation scores had a better prognosis.

Lower levels of psychopathology and low scores on the personality dimensions of inhibitedness, emotional dysregulation, and compulsivity, also predicted a better outcome.

In terms of the effects of AED on outcome, the authors report that in patients with PNES only, the continuation of AED is associated with persistence of attacks and inability to lead an independent life.

Methodological quality

The background and objectives of this study were clearly explained in the introduction; specific research questions, study design and different time lines were well described.

In terms of eligibility, the diagnostic criteria for epilepsy and PNES were clear, however, only just over half of the subjects had the diagnosis of PNES confirmed by video-EEG, although alternative measures were taken to ensure patients had as accurate a diagnosis as possible.

A potential source of systematic error in the study was the high percentage of patients that had the coexisting diagnosis of epilepsy. From a postal questionnaire it would be impossible to determine what kind of attack was being reported by the subjects, whether epileptic or not.

The reasons for choosing specific outcome measures were clearly argued and the different sources of data well described. There was no evidence, however, that there was a system in place to minimise bias when placing subjects into the different outcome groups.

The management of a large proportion of subjects as inpatients with PNES is unusual and probably reflects the characteristics of the German health service. The majority of subjects were treated as in-patients, some under neurologists and others in psychiatric units. From a methodological quality point of view there was also no evidence that any specific treatment protocol had been used.

The statistical tests used are appropriate and well described and the analysis addressed the issue of multiple testing.

The number and characteristics of participants at each stage of the study were clearly reported. As shown in table 2.2, one of the main problems of the study

was the number of responders, which was lower than 60%. Although, in terms of basic clinical and demographic data, responders appear similar to patients lost to follow up, the two groups could have been very different in terms of outcomes and psychological profile.

Considering the large amount of data presented the results were clear with helpful tables illustrating the main findings.

The discussion clearly summarised the main findings as well as acknowledging the limitation and potential bias of the paper.

2.5.6. Paper 3(b)- Measuring outcome in psychogenic nonepileptic seizures: how relevant is seizure remission? (Reuber M., Mitchell A.J., Howlett S, Elger C.E).

This was another study from the postal questionnaire with the same data and sample but a different research question. The aim of this second paper was to investigate the validity of attack remission as a single outcome measure by investigating the correlation between attack freedom and social adjustment. The study found that attack freedom could not be used as a comprehensive measure of a good outcome.

This study only included patients with PNES only and investigated potential differences between patients in remission or not at follow up. It was found that patients in remission were as likely as patients that continued to have attacks to remain on AED. This was a direct comparison between the relevant groups (n=86) using the Chi square, a more robust test than the one used in the original paper where the authors looked for significant relationships between many factors including persistence of AED and three different outcome categories .

2.6. Discussion

The papers included in the present systematic review are all observational and from that point of view none of the studies are protected against bias. As shown in table 2.3, all samples were drawn from tertiary referral centres and therefore from a highly selected population.

None of the studies provided a scientific rationale for the chosen sample size. For the purpose of quality assessment, we chose the cut-off of 75 subjects which by general convention is sufficient to detect a moderate effect size (Cohen, 1992). However this was only a rule of thumb as there was substantial heterogeneity of patients and clinical settings and no study was specifically powered to detect changes in outcome between patients who remained on or off AED.

In terms of the validity of the studies, factors other than the absolute sample size also need to be considered. For our methodological quality criteria, a good study would only include patents with video EEG confirmation of PNES and exclude patients with co-morbid epilepsy (table 2.3). In the study by Reuber et al., only 55% of the sample had the diagnosis confirmed by video EEG, and 60% had coexisting epilepsy - resulting in a much smaller, valid sample. Conversely, the study by Bode et al, has the smallest, though 'purest', sample from this point of view, since all patients had video EEG confirmation and subjects with coexisting epilepsy were excluded.

Response bias is also an issue for the paper by Reuber et al., where the response rate was less than 50% compared with the almost 80% from the study by Bode et al.

The variability on the length of follow up times, within subjects, varied between months to several years in all three papers. There is evidence that outcomes are better in the short term (months to two years) and that studies with follow up times over 5 years report worse results, particularly for psychosocial outcomes (Farias et al, 2003; O'Sullivan et al, 2006).

As shown in table 2.3 another of our quality criteria was whether the length of follow up was long enough to detect changes for all the outcomes of interest. Changes in mood or attack frequency can be detected at a shorter follow-up, compared to vocational status or medical disability, which may take years. The paper by Carton et al included patients from 6 months after the diagnosis, which is probably too short and, although the other two studies assessed patients at

least a year after the diagnosis, there was large variability in the length of follow up within samples.

A common problem and one of the main weaknesses of the three papers is the lack of definition and standardisation of the intervention. There was no management protocol in any of the studies, with high variability in how subjects were managed within and between studies. Considering that these were outcome studies, the fact that only some patients may have had potentially effective interventions makes the interpretation of results difficult.

When evaluating and weighing up the different studies, the issue of outcome in patients with PNES is complicated by the fact that there is no clear definition of what constitutes a good outcome. There is increasing evidence that attack reduction or even attack freedom is not valid as the only measure of a good outcome; and that more comprehensive measures, taking into account social adjustment and psychological status, have more validity when assessing the outcome of patients with PNES (Reuber et al, 2005; Quigg et al, 2002; LaFrance et al, 2006).

Reuber et al's definition of a good outcome was clear and comprehensive, including measures of social adjustment. In contrast, Bode et al. defined a good outcome as any reduction in attacks, which cannot be considered a valid measure since most outcome studies report reduction of attack frequency following the diagnosis. Most patients with a good outcome in this latter paper would be classified as having a poor outcome in the other two studies.

Another factor that will affect the validity of the selected studies is the percentage of patients on AED, since this is our outcome of interest. From this point of view, the selected sample by Bodde et al. had only 3/22 (15%) patients on medication, which clearly affects the power to detect any significant differences in terms of outcome of patients on or off AED.

2.7. Summary

Of the three selected papers for the present systematic review, the two largest studies report an association between continuing AED and a poor outcome of PNES; whereas the smallest and least powered study reported no association.

The results of the present review appear to support our hypothesis however, because of the described methodological limitations of all the studies we can't conclude that any correlation between taking AED and an adverse outcome was free from confound or bias.

The quality of most of the research on PNES is limited, partly reflecting the practical and methodological difficulties when studying this group of patients. Carrying out outcome studies in this area has particular challenges due to the relatively small incidence of the disorder, the heterogeneity of the group and the absence of a universal treatment approach (LaFrance et al, 2006).

The current published studies on outcome of PNES (including our selected papers) are difficult to compare and interpret since there is great variability amongst the selected populations, as well as a lack of consensus on what is a good outcome or a reasonable follow up period (Bowman & Markand, 2005; LaFrance et al, 2007).

These studies, however, recognised the potential effect that taking AED may have on the outcome of PNES. The Carton et al study presents some qualitative data where continuation of AED reflects patients' and GP's views on the cause of the disorder, in this case "epilepsy" rather than PNES (Carton et al, 2007).

Following this systematic review we are unable to conclude whether failing to withdraw AED has an effect on the outcome of PNES, however the data does suggest that a substantial number of patients with PNES continue to take AED and that these subjects have a poorer outcome. A randomised controlled trial would be the only way to establish if withdrawing AED at diagnosis contributes to a better outcome in patients with PNES.

Chapter 3:

Going forward: Prologue to the original thesis research

3.1. Aims and objectives of the thesis portfolio

In the overview in chapter one, evidence was presented to show that PNES, within certain settings, is not an uncommon disorder entailing a major impact on patients' mental, physical health and social functioning (Breuer et al, 1998; Bowman & Markand, 2005). Since the majority of these patients are wrongly diagnosed as having epilepsy, most are treated with AEDs often for many years. As described in chapter 1 (page 16), the routine use of AED in this group of patients has important and overwhelmingly negative consequences.

There is a lack of evidence for an effective treatment in the current literature (Brooks et al, 2002). The scarce evidence for the management of PNES is not surprising considering that PNES is a symptom of a variety of underlying causes, making the formulation of a single theoretical framework upon which to base any particular management strategy very difficult. The wide range of treatments described in small observational studies, possibly reflects the heterogeneity of the patient group.

Although a definitive, universal psychotherapeutic intervention cannot be recommended this does not belie the fact that PNES is a condition associated with substantial harm that has to be recognized and diagnosed. There is reason to believe that if performed confidently and sympathetically the delivery of the diagnosis in association with a clear 'undiagnosis' of epilepsy can constitute an effective intervention in itself. Reuber in particular has questioned the likelihood or appropriateness of elaborating a single management strategy and proposes a stepped care approach with the essential initial generic step including the presentation of the diagnosis (Reuber, 2008).

The present thesis aims to focus on the component parts of this initial intervention. Since most patients with PNES are initially thought to have epilepsy and treated inappropriately with AED, the withdrawal of medication should be part of this initial process, but is sometimes delayed because of a variety of background factors and concerns outlined below. The primary hypothesis of this thesis is that withdrawing AED following the diagnosis of PNES is in itself a therapeutic step and enhances the positive effects of a clear delivery of the diagnosis.

Although the effect of diagnosis and medication withdrawal was elucidated to an extent by the systematic review in chapter 2, this was not the specific focus of any of the papers and the role of a clear diagnosis and medication withdrawal was obscured by methodological and clinical heterogeneity, a lack of explicitness or standardistion of the intervention, loss to follow up and differences in reported outcomes. Overall, although continuing inappropriate prescription of AED was associated with a poor outcome this could not be shown at a level that would endorse the specific efficacy and safety of medication withdrawal as an intervention in patients with PNES.

There is some evidence to suggest that the intervention of withdrawing AED in this group of patients is perceived as unsafe by clinicians (O'Sullivan et al, 2006), which would partly explain why such high numbers of patients with PNES are left on AED. Concerns exist regarding the accuracy of the diagnosis and the recurrence of possible epilepsy following the withdrawal of medication, in particular the precipitation of potentially fatal status epilepticus. These concerns together with the perception that leaving patients with PNES on AED is not harmful would naturally incline physicians to err on the side of caution and not withdraw medication following the diagnosis of PNES (Reuber & Elger, 2003c).

The issue regarding the accuracy of the diagnosis has been extensively researched and there is good evidence that an accurate diagnosis is possible with the right expertise and diagnostic tests. For the purposes of the current thesis all subjects were diagnosed as suffering from PNES on the basis of the current gold standard; video EEG confirmation of a clinical diagnosis by a clinician experienced in the diagnosis and treatment of both epilepsy and PNES.

The safety of AED withdrawal is another issue and in this case there is no evidence on the absence of harm of this intervention. Establishing the safety of AED withdrawal in this patient group has to precede any study on the possible therapeutic effects of withdrawing medication.

The first study therefore aims to answer the question of whether withdrawing AED in patients with PNES is a safe intervention. For this purpose an observational study was conducted, consisting of a case series of a group of

patients with NES followed up over a period of twelve months after AED withdrawal.

The first study can be conceptualised as a Phase one trial preliminary study directed toward demonstrating the safety and tolerability of an intervention with regard to the risk of untoward health related events. The intervention in this case would be the diagnosis of PNES and subsequent AED withdrawal, the untoward event would be either the misdiagnosis of epilepsy as PNES or the 'induction 'of epilepsy by withdrawal of AED.

In this context an observational study was considered adequate and methodological rigour was maintained by ensuring that the design included the points below:

- The study was based on a clinic population of the only regional service assessing patients with PNES from primary and secondary care
- Standardised intervention
- Clear protocols for diagnosis and drug withdrawal
- Clear inclusion criteria and well defined outcomes

As well as determining the safety of the intervention the observational study was an opportunity to show that for the purpose of generalisability and replication a reliable and valid diagnosis of PNES could be made and withdrawal of medication undertaken with the resources available to other tertiary centres.

Once there was evidence that withdrawing AED in patients with PNES was a safe intervention it was possible to proceed to addressing the next research question of whether withdrawing AED has a positive therapeutic effect.

As outlined above the systematic review of the literature (chapter 2) revealed that the only evidence for the possible effects of discontinuation of AED following the diagnosis of PNES, comes from three observational studies of limited quality and with conflicting results. Further observational work along the same lines would replicate the flaws identified in the review and only an experimental design would be likely to further investigate the effect of AED

withdrawal in a way that would be free from confounding and bias as far as possible.

The specific choice of a randomized controlled design with groups randomized to delayed and immediate withdrawal was justified as follows:

- The natural history of PNES is not so clearly defined that a before and after methodology would be adequate as the possibility of spontaneous recovery could not be discounted or anticipated in a predictable way.

- Only randomization to parallel groups could address the known and probable unknown confounders in this heterogeneous disorder.

- In terms of the basics of study design and anticipating likely methodological and practical issues most of the current evidence on AED withdrawal had to be extrapolated from epilepsy research. Although most of this evidence is irrelevant to PNES, design and methodological issues are similar and in particular gives clear guidance on the timing, dosage schedules and monitoring of drug withdrawal. A randomised controlled trial comparing the effects of withdrawing AED immediately following the delivery of the diagnosis versus a delayed withdrawal appeared the most appropriate study design and had clear and relevant precedents in the epilepsy literature.

- Blinding of patients to their status as regards delayed or immediate discontinuation was not possible, or desirable. The aim of the study was to ascertain the efficacy of two plausible alternatives. However, although subjects had to be aware of their status, neither arm was aware which intervention was the control and which the intervention.

The study was designed to include a replication phase on the effect of AED withdrawal.

There is evidence that reduction or absence of attacks is not valid as the sole measure of a good outcome in patients with PNES (Reuber et al, 2005). Psychological and particularly social outcome measures are frequently reported

as poor even in patients where attacks are controlled or significantly reduced. Hence, although the trial took attack freedom and frequency as its primary outcome, a comprehensive range of psychosocial measures were included to allow a more detailed exploration of the psychosocial aspects of PNES. Care was taken to include measures along the lines used and reported by other workers in the field to allow comparison between our relatively prescriptive and behavioural paradigm and the approach of other workers.

The systematic review of the literature also highlighted the methodological flaws of many of the outcome studies on PNES; in particular the inclusion of epilepsy patients, the absence of a standardised intervention, and the variable length of follow up amongst subjects. By the end of the replication phase of the RCT data was available for a group of prospectively collected patients, subject to the same assessment and intervention and followed up for the same length of time.

In summary, this thesis will attempt to answer the main research question of whether AED withdrawal has a therapeutic effect on patients, utilizing a combination of study designs, in three stages.

Overall the research portfolio can be conceptualized in the following way: an initial phase one trial to investigate safety aspects of the AED withdrawal intervention; a phase 3 trial aiming to establish potential therapeutic effects of AED withdrawal; and a third paper which can be seen as an open label surveillance study aiming to obtain a detailed and comprehensive picture of outcome.

The thesis portfolio includes the following papers:

- A systematic review of the literature on evidence of the effects of AED on the prognosis of PNES.

- An observational study on the safety of AED withdrawal of 78 patients with psychogenic nonepileptic seizures.

- A Randomised Controlled Trial comparing the effects of immediate versus delayed withdrawal of Antiepileptic drugs withdrawal in patients with psychogenic nonepileptic seizures.

- The psychosocial outcomes of 24 patients with psychogenic nonepileptic seizures 18 months after the diagnosis.

The main objectives of the thesis are:

- To establish the clinical safety of antiepileptic drug withdrawal in patients with PNES.

- To investigate the potential therapeutic effects of antiepileptic drug withdrawal, in patients with PNES.

- To explore short-term psychosocial outcomes of patients with PNES following a management strategy which includes AED withdrawal.

Chapter 4:

Can we safely withdraw antiepileptic medication in patients with psychogenic non-epileptic seizures? Descriptive analysis of outcome data on patients with PNES treated with antiepileptic drugs.

An abbreviate version of the contents of this chapter are published as follows:

Oto, M., Espie, C., Pelosi A., Selkirk, M. Duncan, R. (2005). The safety of antiepileptic drug withdrawal in patients with non-epileptic seizures. *Journal of Neurology ,Neurosurgery and Psychiatry*, 2005 ,76(12);1682-1685.

4.1. Abstract

Background: Psychogenic nonepileptic seizures (PNES) or pseudoseizures are psychologically mediated attacks that resemble and are often mistaken for epilepsy. Most patients are initially misdiagnosed as having epilepsy and inappropriately treated with AED. A significant percentage continues to receive AED even after the diagnosis of PNES has been confirmed, partly reflecting reluctance from the clinicians that perceive the withdrawal of AED as potentially unsafe.

Objective: To determine whether withdrawal of anticonvulsant medication (AED) can be carried out safely in patients with psychogenic non-epileptic seizures.

Methods: Prospective evaluation of safety and outcome in 78 patients with PNES who satisfied a standardised set of criteria for the diagnosis of 'no epilepsy'.

Findings: The patients were taking from 1-3 AED. Sixty four patients were withdrawn as outpatients, 14 as inpatients. Five patients stopped their medication abruptly, and two had AED inappropriately restarted and had to be withdrawn again. Otherwise all patients adhered to withdrawal schedules. A new type of attack was seen in 3 patients, in all 3 cases complex partial seizures. In two of these cases the existence of controlled epilepsy was unsuspected. PNES frequency declined in the group as a whole over the period of the study (follow up 6-18 months), in all individuals except for 8 patients in whom there was a transient increase. Fourteen patients produced new physical symptoms during withdrawal.

Interpretation: With appropriate diagnostic investigation and surveillance during follow up withdrawal of AED can be achieved safely in patients with PNES.

4.2. Introduction

Psychogenic nonepileptic seizures (PNES) are psychologically mediated attacks that resemble and are often mistaken for epilepsy Diagnosis and management of PNES represents a significant clinical problem, since patients may present to a variety of doctors with attacks that are mistaken for and treated as epileptic seizures or status epilepticus (Howell et al, 1989; DeToledo et al, 2000; Reuber et al, 2002).

Most patients with PNES do not have epilepsy, however up to 80% are exposed to at least one antiepileptic drug (AED) leading to morbidity and mortality (Benbadis, 1999). Even after the diagnosis of PNES is confirmed and no evidence of epilepsy has been found, 20-44% patients remain on a single or multiple AEDs (Reuber & Elger, 2003c; O'Sullivan et al, 2007; Hall-Patch et al, 2010).

There is also evidence that this paradoxical prescribing practice is not an exclusive phenomenon of PNES but also applies to other medically unexplained symptoms where patients are left on medication despite no evidence of a physical problem (Barsky & Borus, 1999; Mayou et al, 2000).

Little attention has been given to the reasons for this group of patients remaining on medication despite a clear diagnosis of PNES, or the possible adverse consequences of drug withdrawal should it take place.

There is a substantial literature however, looking at AED withdrawal in the context of patients with proven epilepsy. The consensus amongst experts in the field is that AED withdrawal should be considered for all patients with epilepsy who have been seizure free for more than two years, even though we have evidence that the average risk of recurrence of epilepsy is between 40 and 60 % within 2 years (Chadwick & Scherokman, 1991).

If a clinician treating a patient with epilepsy is willing to accept a risk of this order, why is there an apparent reluctance to withdraw AED in patients who did

not have epilepsy in the first place? It seems that the risks and benefits of AED withdrawal in patients with PNES are appraised in a very different way.

There are various good reasons why patients with PNES in whom there is no evidence of epilepsy, should not be prescribed AED's. For example, avoiding iatrogenic harm, particularly teratogenicity, in a population with a majority of women of childbearing age (Sigurdardottir & Olafsson, 1998; Szaflarski et al, 2000, DeToledo et al, 2005). There is also some evidence that medication may exacerbate PNES (Damaschke et al, 1988; Niedermayer et al, 1970) and that continuation of AED after diagnosis may be associated with a poor prognosis (Reuber et al, 2003b). There are also obvious cost implications of giving unnecessary expensive medicines (Martin et al, 1998) and in the longer term potential medico legal consequences.

Despite all of the above, the reality is that many patients with PNES are maintained on AED long after the diagnosis. Although there is little published research in this area, some factors may explain the reasons behind the reluctance to withdraw medication in this group of patients as summarised in table 4.1. One important factor to clinicians may be a lack of confidence in the diagnosis and concerns about missing possible underlying epilepsy, with consequent perception that AED withdrawal is associated with significant risk of serious adverse outcomes such as status epilpticus. Even when this is not the case, drug withdrawal does entail a non medical explanation for the attacks leading to a potential collision with patients expectations (Doust & DelMar, 2004).

In order to determine whether it can be safe to withdraw AED in patients who have PNES only, we conducted an observational study investigating the outcomes of a group of patients with video-EEG confirmed diagnosis of PNES and no evidence of epilepsy who were withdrawn form AED's.

Table 4.1: Clinician concerns of AED withdrawal.

	Possible clinician concerns of AED withdrawl
1	Accuracy of the diagnosis of PNES or unrecognised underlying epilepsy
2	Morbidity and mortality associated to AED withdrawal if patient has unrecognised epilepsy
3	AED withdrawal producing an exacerbation of psychological symptoms if AED were acting as psychotropic drugs
4	Exacerbation of PNES or symptom substitution in patients who somatise when removing the diagnosis of epilepsy and AED

4.3. Methods

The current study was based at the Southern General Hospital PNES clinic, which is part of the West of Scotland Epilepsy regional unit.

As part of routine clinical practice, all patients had an extensive clinical assessment including detailed description of the events by patients and eyewitness. All subjects had video EEG confirmation of the diagnosis by recording all typical events. Once the clinical diagnosis of PNES was confirmed, a concomitant diagnosis of epilepsy was regarded as excluded if the following criteria were satisfied:

- All current types of events described were recorded and identified as PNES
- No description of past events rising suspicion of epilepsy
- No evidence of events during childhood
- No inter-ictal epileptiform abnormalities on EEG

.

Initially all subjects were investigated as out-patients with “Short Video EEG” with suggestion (McGonigal et al, 2004a) and if this investigation was not conclusive patients were then admitted to the ward for video EEG.

The final diagnosis was always reached by consensus of at least three clinicians (including a neurophysiologist). The more complicated cases were formally discussed in a team clinical meeting.

Once a firm diagnosis of PNES was made, patients were seen at the clinic where the diagnosis was delivered in a non-judgmental and supportive manner.

We developed a written information leaflet on PNES which was given to the patients and relatives at this point (appendix C). In terms of this written information, our intention was to ensure that it was relevant and meaningful to the patient group.
Going by clinical experience we were aware of a specific range of questions frequently asked by patients and relatives at the clinic These questions were used as the basis of the leaflet..

The author also recorded all questions asked by 20 new patients and their relatives attending the PNES clinic and these were reviewed and thematically grouped to establish any dominant themes. The themes that emerged were:

- The nature and causes of the disorder;
- Diagnostic tests;
- Treatment.

Answers to these questions, combined with ourclinical experience and current research evidence were then drafted as the information leaflet

To assess the validity of the questions and responses, the information sheet was passed for comment to the epilepsy multi-disciplinary team and 10 consecutive patients at the clinic. The amended information sheet was then piloted at the PNES clinic with further patient feedback taken into consideration.

Comments, including the use of terminology, the clarity and relevance of information and presentation style, were incorporated into a final version.

AED medication was withdrawn in all patients with a final diagnosis of PNES-only and the drugs tapered sequentially following a standard withdrawal protocol created by the authors based on clinical experience of AED withdrawal in

epilepsy patients during neurosurgical assessment (appendix D). During the medication withdrawal patients were reviewed at a minimum interval of 3 months by the epilepsy specialist. In difficult cases, in particular when coexistent epilepsy could not be confidently excluded, medication was withdrawn in an in-patient setting.

Information on all patients seen at the PNES clinic was prospectively and systematically collected in a comprehensive database. Follow up information was collected at 6 and 12 months of the completion of the AED withdrawal.

The main outcomes of interest were the potential risks in terms of morbidity and mortality associated with AED withdrawal as presented in table 4.1. Other outcomes recorded were reduction of attacks and AED status at follow up.

Data were entered prospectively into an Access database on a dedicated PC and were regularly checked for completeness and accuracy. For the current descriptive study the information was taken from this Access database and for the purpose of analysis the data was transferred to SPSS.

4.4. Sample

Of the total cohort of 235 consecutive patients referred at the clinic between Jan 2000 and Jan 2003, 184/235(78.2%) had a video EEG confirmed diagnosis of PNES and satisfied criteria for “no epilepsy”. The reminder were still either awaiting video EEG (25/235, 10, 6%) at the end of the study, or had coexisting epilepsy (26/235, 11.1%).

Of the 184 subjects with confirmed diagnosis of PNES alone, 99 (53.8 %) were taking AED. The remaining 38(20.6%) had never been on AED or their drugs had been withdrawn before clinic attendance (47/184, 25.5%).

Of the 99/235 patients with the diagnosis of PNES-only that were taking AED, 78/99 were eligible for the study. The remaining 21/99 (21.2%) patients were excluded for the following reasons; 12/99 (12%) patients were lost to follow up, 2/99 (2%) patients refused to come off medication, and 7/99 (7%) were still reducing AED at the time of the analysis (Table 4.2).

Table 4.2: Reasons for participant exclusion.

Patients on AED	N=99	%
Lost after diagnosis	12	12
Still reducing medication	7	7
Patient refused to withdraw	2	2
Withdrawal completed (Study population)	78	78

4.5. Results

4.5.1. Antiepileptic drug status

Over half of the patients had been started on AED by a neurologist or general physician and we were unable to ascertain who had commenced prescription in 25% of patients. At the time of referral, patients were taking a median of 2 AED (range 1-3); 28/78 (36%) were on more than two AED and 20/78 (28%) reported side effects on their medication.

When questioned about the impact of AED on their attacks, 4/78 (5%) patients felt worse on starting AED but others reported feeling better on the medication 6/78 (8%) or a temporary improvement when the drugs were started 27/78 (35%). The rest 36/78 (46%) did not report any change.

4.5.2. Antiepileptic drug withdrawal

All study patients were instructed to come off medication. In the majority of cases this was done as an out-patient by giving clear instructions to the patients and their GP, with regular review at the clinic. Only 14/78 (18%) patients were admitted for drug withdrawal, the reason for admission were as outlined below.

- Patients with a possible underlying well controlled epilepsy (4/14). All these patients had current or past pathology that could be associated with epilepsy (e.g. severe head injury, brain tumour, meningitis).
- Patients in whom standard diagnostic procedures had failed to confirm the diagnosis (5/14). In all these patients medication was withdrawn during admission as part of the diagnostic process.
- Patients with mild learning disability (5/14). This group had difficulties understanding the diagnosis of PNES and the withdrawal schedule. In addition, patients and their carers also expressed anxiety about coming off medication. Three of these patients had failed to complete previous attempts of withdrawal as out-patients and all were regular users of the emergency services.

The remainder of the cohort (64/78), were able to successfully complete AED withdrawal as an out-patient: Of the patients coming off medication at home, 57/64 (89%) were able to follow the slow titration protocol as planned. Five patients (5/64, 7.8%) stopped medication as soon as the diagnosis was given and in two patients (2/64, 3%) the medication was suddenly stopped by their GP. None of the patients who stopped medication suddenly (7/64, 10.9%) reported any adverse effect. There was no evidence of withdrawal seizures (although none were taking barbiturates or benzodiazepines).

4.5.3. Demographic and clinical characteristics

Fifty-seven out of 78 (73%) were female, 34/78 of whom were of child bearing age, the mean age at the time of presentation at the clinic was 39.6 years (sd14.3) and the mean age of onset of events was 32.4 year (sd15.4). Nine out of 78 (11.5%) patients had a mild learning disability. Patients had been referred to the clinic mainly by epilepsy specialists or neurologists 60/78 (77%). As shown in table 4.3 the above figures were comparable with the rest of the PNES clinic population.

Table 4.3: Characteristics of the study population.

	Study population n=78	Clinic population n=219, Confirmed diagnosis of PNES-only
Gender distribution		
FEMALE	57 (73%)	166(76%)
MALE	21(27%)	53(24%)
Learning disability	9 (11.5%)	18(8%)
Source of referral		
NEUROLOGY/EPILEPSY	60 (77%)	145 (66%)
GP	8 (10%)	42 (19%)
GEN PHYSICIAN	7 (9%)	19 (8.6%)
PSYCHIATRIST	3 (3.8%)	10 (4.5%)
Missing data	0	3 (1.3%)
Mean age at referral (years)	39.6 (14.3)	40 (14.1)
Mean age first event (years)	32.4 (15.4)	33 (14.4)

At the time of referral this represented a complex group of patients. There was a high prevalence of morbidity of all types; as a result of the direct physical consequence of the 'seizures', associated psychopathology, as well as a very high prevalence of coexistence of other medically unexplained symptoms (table 4.4)

Table 4.4: Patients overall characteristics at baseline.

PATIENTS CHARACTERISTICS AT REFERRAL	N=78	%
Psychopathology:		
CONTACT WITH PSYCHOLOGY/PSYCHIATRY	**44/78**	56.00%
DEPRESSION	**44/78**	56%
SUICIDE ATTEMPTS	**15/78**	19%
SELF-HARM	**7/78**	9%
MEDICALLY UNEXPLAINED SYMPTOMS	**56/78**	71.70%
Impact of PNES		
INJURY THROUGH ATTACKS	**26/78**	33%
ATTACK FREE FOR >1 MONTH	**23/78**	29%
PSEUDOSTATUS	**23/78**	29%
VISIT TO A&E	**43/78**	55%
Social impact:		
BENEFITS	**53/78**	68%
EMPLOYED	**9/78**	11.50%

4.5.4. Outcome after AED withdrawal

At follow up we had data up to 6 months in all patients. In 56/78 (78%) patients we had data up to 12 months and for 28/78 (36%) we had follow up information at 18 months after AED withdrawal.

As outlined above we looked at the following end points: evidence of emergent epilepsy, AED restarted, frequency of PNES, newly reported symptoms and morbidity as a result of AED withdrawal

4.5.4.1. Evidence of coexisting epilepsy after drug withdrawal:

Three patients 3/78 (3.8%) presented with a new type of attack, that turned out to be epileptic, in all cases conforming to complex partial seizures.

The coexistence of ES as well as PNES was promptly recognised in these three patients and AED medication re-started, bringing epileptic seizures quickly under control in all cases.

In one case we had high suspicion of coexistence of underlying ES, therefore diagnosis and AED withdrawal was done during a prolonged in-patient admission. The patient did not present with the new attacks until a year after AED withdrawal. .We had not suspected coexisting epilepsy in either of the other two cases; neither had predisposing factors or a childhood history of epilepsy and the only events reported by patients and witness were the ones recorded during video EEG.

In terms of outcome, ES was controlled in all patients after restarting AED. In two cases this represented a reduction to mono-therapy from the two AED they were taking at referral. All three patients accepted the dual diagnosis, two remain free of PNES and the third had a substantial reduction.

4.5.4.2. AED restarted:

Two patients had been restarted on AED, in one case by the GP in view of persistence of events and for the other patient as a result of attendance at A&E. In both cases medication was withdrawn again successfully.

In one patient, at the first follow up visit (6 weeks), we noticed that the GP had continued to issue repeat prescriptions of AED. Contacting the GP over the phone as well as through a letter rectified this.

4.5.4.3. Frequency of PNES after drug withdrawal:

There was a significant and sustained reduction of attacks over time, whether attack frequency data was analysed by changes between groups, within individual subjects, or by the total number of patients attack free (see table 4.5).

Table 4.5: Changes in attack frequency from baseline.

Attack frequency per month	mean	SD	median	RANGE	N
AT REFERRAL	22.23	30.78	15	0.5-180	N=78
6 MONTHS FOLLOW UP	13.01	38.46	2	0-300	N=78
AT 12 MONTHS FOLLOW UP	10.66	36.4	0	0-250	N=56
AT 18 MONTHS FOLLOW UP	3.96	11.05	0.75	0-60	N=28

A Wilcoxon signed rank test showed that there was a significant difference in attack frequency between referral and six month follow up ($p<0.001$). Fifty-six patients were followed up at 12 months. These patients had significantly less attacks than at referral ($p<0.001$) or at 6 month follow up ($p<0.001$). Twenty-eight patients were followed up at 18 months. Attack frequency was less than at referral ($p<0.001$) and at 6 months ($p=0.001$).

At 12 months after AED withdrawal, 35 of 71 patients (49%) had been free of attacks for more than two months.

An increase of frequency of their usual events 6 months after AED withdrawal was reported by 8/78(10%) patients. In most patients (7/8) this represented an increase of over 50% with a median of 15 attacks per month at referral versus 30 at 6 months. This was a transitory effect in all cases and no particular action was required for any of these patients.

4.5.4.4. Morbidity and mortality after AED withdrawal:

As shown in table 4.6, no serious adverse events, including admissions to intensive care (ITU) or death, were reported.

Table 4.6: Morbidity and mortality after AED withdrawal.

Morbidity and mortality after AED withdrawal	**N=78**	**%**
Pseudostatus (prolonged attack treated with benzodiazepines)	4/78	5%
Status epilepticus	0/78	0%
Reporting injuries for the first time	0/78	0%
Continue to sustain minor injury	10/78	12.80%
Admissions to ITU	0/78	0%
Death	0/78	0%

Our definition of pseudostatus was a prolonged PNES thought to be epileptic and treated by administering AED medication. Twenty three patients (29%) had episodes of pseudostatus before withdrawal, but only four had episodes afterwards (all had previous episodes). Ten patients (13%) continued to report minor injury (bruises and grazes) after withdrawal.

4.5.4.5. Newly reported medical and psychological symptoms:

Fourteen patients (18%) reported new symptoms, while three (3.8%) reported an exacerbation of previous symptoms, and nine (11.5%) had investigations for new complaints. In two patients the new complaint (chest pain and fatigue) represented the main source of disability and health care utilisation at follow up. Ten patients (13%) were started on new drugs, in most cases (6/10) an antidepressant drug (see table 4.7).

Table 4.7: Report of new clinical events after AED withdrawal.

New physical complaints after withdrawal	**N=78**	**%**
New physical symptoms	14/78	18%
Exacerbation of long standing symptoms	3/78	3.80%
New medication started	10/78	12.80%
Undergoing new investigations	9/78	11.50%

As shown in table 4.8, five patients (6.4%) reported new psychological symptoms: low mood (three patients), irritability, and anxiety however, none required psychiatric intervention. One patient with a past psychiatric history self harmed transiently after AED withdrawal.

Table 4.8: New reports of psychological complaints following AED withdrawal.

New psychological complaints following AED withdrawal	**N=78**	**%**
New symptoms	5/78	6.40%
Self harm	1/78	1.20%
Suicide attempts	0/78	0%

4.6. Discussion

To our knowledge this study is the largest observational study of the outcome of AED withdrawal in this complex population. Although the study population represents a selected sample, the general characteristics of the group were comparable with the rest of our clinic patients and with those described in most reports on PNES (Moore & Baker, 1997; Reuber & Elger, 2003c; O'Sullivan et al, 2007) although the mean age of onset of events of our group was at the upper end of the range of most studies.

Despite our selected sample, we do feel that with this study we have been able to present data that might address the concerns that arise in the care of patients with PNES, in particular the safety or otherwise of withdrawing AED.

As well as data on the safety aspects of AED withdrawal, the current study provides some interesting information on other aspects of AED prescription in patients with PNES. In terms of the effect that prescribing AED had on these subjects, it is interesting to point out that almost half of the patients reported some benefit at least initially from the AED and only a minority reported an exacerbation of attacks. Transient response to AED in terms of a reduction of PNES frequency has been described by some authors (Bowman & Markand, 1996; Sirven & Glosser, 1998) but an exacerabtion of attacks with AED is more often reported in the literature, being cited as a distinguishing factor between ES and PNES. However this was not the case in our group.

In terms of patient safety, the main outcome of the study, two factors are critical in our view: the confidence with which possible underlying epilepsy is excluded, and the quality of monitoring of the patients during and after AED withdrawal.

The best indicator of the accuracy of criteria for excluding epilepsy is whether or not epileptic seizures occur on withdrawal of AED. Interestingly, relapse occurred soon after withdrawal in the two patients, in whom it occurred unexpectedly, indicating that these patients had controlled epilepsy rather than epilepsy in remission. In the third patient, who had a history of resected frontal low grade glioma, complex partial seizures occurred just over a year after AED withdrawal. This suggests that either a pre-existing epilepsy was in remission or

that a new epilepsy had arisen (not inconceivable given the past history), and suggests the need to monitor patients over an extended period.

Our study ended in January 2003 and no other patients have since had epileptic seizures. This is compatible with the results of studies of relapse rate in patients with epilepsy following AED withdrawal, which shows that the majority of relapses occur within six months after withdrawal (Chadwick & Scherokman, 1991).

Our criteria for excluding epilepsy are straightforward, and are applied with care, particularly in the matter of being sure that descriptions of all events are as accurate as they can be, and that they are carefully compared with the events that have been recorded. Nonetheless, when a patient has controlled epilepsy and has not had an epileptic seizure for some years, it may be unrealistic to expect accurate descriptions of early events in all cases. This may particularly be the case if the original events were complex partial seizures that were promptly controlled, and when the present PNES are much more frightening and dramatic in the eyes of relatives.

Despite the absence of recurrent major seizures in our series, it is clear that close supervision of the withdrawal process is an important safety measure, not only to ensure that the occurrence of epileptic seizures is rapidly detected and communicated to the PNES team, but also to ensure that patients (and doctors) comply with withdrawal schedules. There is evidence that re-introduction of AED in this group of patients is not uncommon, presumably in association with a lack of acceptability of the diagnosis by patients, carers and GP's (Lempert et al, 1990; Walczak et al, 1995; Jongsma, 1999; O'Malley, 2000). In the current study great effort and time was devoted to promote the acceptance of the diagnosis as intrinsic to the success of the intervention .

We ensured that; patients, relatives and General Practitioners received clear and consistent information in terms of the diagnosis and the importance of coming off medication. Extra appointments were offered if concerns arose from the patients or the relatives regarding the diagnosis or medication withdrawal. Clear and detailed letters were sent to the GP's and for a few patients letters were also sent to their local Accident and Emergency to forestall inappropriate treatment of apparent status epilepticus.

For example, one of the patients included in the study was re-started on AED by his GP after he reported an increase of nonepileptic attacks as the medication was withdrawn. Because of the frequency of follow up contacts, we were able to quickly identifiy and address the problem. After establishing that there was no evidence of emerging epilepsy, clear explanation and reassurance were given to the patient together with further instruction to withdraw AED. To ensure the success of the second attempt at drug withdrawal the patent's GP was contacted by phone to clarify any concerns and this was followed by a letter.

Over-treatment of epileptic seizures is common in patients who also have PNES (Blumer et al, 2006). For the small number of our patients in whom epileptic seizures appeared after AED withdrawal we were able to re-introduce AED treatment sensibly, resulting in mono-therapy and lower doses.

The level of reporting of new physical or psychological complaints following AED withdrawal was low in our patients, particularly considering the high rates of reported psychopathology and physical symptoms at presentation. In those who reported new medically unexplained symptoms, it was unclear whether this was associated with the removal of the diagnosis of epilepsy, with withdrawal itself, or with the reduction in PNES frequency that took place at the same time. Medically unexplained symptoms are common in patients with PNES (Lempert & Schmidt, 1990; Ettinger et al, 1999; Reuber et al, 2003) and it is perhaps unsurprising that the removal of one psychogenic symptom might sometimes provoke the appearance of another.

Overall our patients had a generally good outcome with a significant reduction in frequency of PNES after drug withdrawal and only a minority of patients reporting an increase. Similar rates of reduction of attack frequency following diagnosis of PNES have been reported in other follow up studies using different methods of diagnosis and management (Ettinger et al ,1999; Selwa et al, 2000; Reuber et al, 2003, Goldstein et al, 2004) which suggests that the reduction is probably a result of multiple factors, of which AED withdrawal is only one. It would require a randomised controlled trial of drug withdrawal to establish the extent to which there is a causal relation between AED withdrawal and a good outcome of PNES and we are in the process of carrying out such a trial.

The MRC AED withdrawal study indicates that a patient who has had tonic-clonic convulsions but has been seizure-free on a single AED for two years has a 60% risk of seizures in the first year after drug withdrawal (Chadwick & Scherokman, 1991). While the number of patients in our study is relatively small, our data suggest a much lesser risk in appropriately selected and monitored patients with PNES, yet patients often remain on AED. We cited some potential adverse consequences of AED in the introduction; it may be worth adding that of the 34 of our patients who were women of childbearing age nine had had pregnancies while on AED.

4.7. Conclusion

Overall, from the point of view of safety, which was the main objective of the study, the outcome of patients after medication withdrawal was positive, with minimal and not serious adverse events. Even for the three patients in whom the diagnosis of epilepsy emerged after drug withdrawal AED withdrawal allowed clarification of diagnosis and rationalisation of treatment.

We conclude that in appropriately selected patients with PNES, and where suitable expertise and monitoring are available, AED withdrawal can be safe. Patients who are thought to have PNES should therefore be referred to appropriate centers.

Chapter 5:

Clinical outcome of a Randomised Controlled Trial comparing the effects of immediate versus delayed withdrawal of Antiepileptic drugs in patients with nonepileptic seizures.

An abbreviated version of the contents of this chapter are published as follows:
Oto. M, Espie CA, Duncan R. (2010) An exploratory randomised controlled trial of immediate versus delayed withdrawal of antiepileptic drug in patients with psychogenic nonepileptic seizures(PNEAs). *Epilepsia*.

5.1. Abstract

Background: Psychogenic nonepileptic seizures (PNES) are psychologically mediated attacks that resemble and are often mistaken for epilepsy. Most patients with PNES are treated with AED and continue to receive medication even after the diagnosis is confirmed. A failure to withdraw AED's may undermine the diagnosis of PNES and hinder adjustment to the removal of the diagnosis of epilepsy and negatively affect outcome.

Main hypothesis: Withdrawing AED following the diagnosis of PNES is in itself a therapeutic step and enhances the positive effects of a clear delivery of the diagnosis.

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Methods: A Randomized controlled trial of AED withdrawal in patients with PNES. Patients were randomized to immediate or delayed (9 months) withdrawal of AED. We recorded attack frequency, changes of the use of emergency medical services and a variety of psychosocial measures at baseline, 9 months and 18 months.

Result: Of 193 patients screened, 38 fulfilled entry criteria, 13 declined participation and 25 were randomised. Fourteen patients were randomized to immediate withdrawal (IW), 11 patients to delayed withdrawal (DW). There was a significant reduction in spell frequency from baseline to 9 months in the IW group but not in the DW group ($p=0.028$). There was a significantly greater reduction in use of rescue medication in the IW group compared to the DW group between baseline and 9 months ($p=0.002$). Emergency healthcare utilization dropped to zero in both groups by the end of the study. Psychological measures reflecting internal locus of control increased significantly more in the IW group ($p=0.005$).

Conclusion: The present study may be regarded as an exploratory exercise and as such has provided a suggestion that withdrawing AED enhances the effect of a clear delivery of the diagnosis. This effect is reflected in a persistent reduction in attack frequency and a cessation of the use of emergency services and medication following AED withdrawal. Importantly none of our data show any negative effects.

5.2. Introduction

Psychogenic nonepileptic seizures (PNES) may be defined as paroxysmal events that resemble and could be mistaken for epileptic seizures, without being associated with any measurable alteration in brain electrical activity. The underlying cause for PNES could be plausibly attributed to psychological processes as opposed to alternative physiological processes such as faints. PNES present to virtually all health care professionals, account for approximately 18% of patients presenting with blackouts and represent a significant management problem to epilepsy specialists (Kotsopoulos et al, 2003).

A variety of psychological interpretative paradigms have been proposed to explain or understand PNES. These range across the traditionally psychodynamic, the strictly behavioural and the eclectically psychosocial, and allude to a variety of psychological mechanisms including dissociation, hysterical re-enactment, learned behaviour and frank malingering (Bowman & Markand, 1996; Gates, 2002; Salomon et al, 2003; Marchetti et al, 2008). As such, the difficulties of assessment of the various treatments, of an already heterogeneous disorder (Lesser et al, 2003; Cragar et al, 2005; Baslet et al, 2010), are compounded by the breadth of approaches adopted. Unsurprisingly, a recent Cochrane review on the behavioural treatment of PNES concluded that there is no reliable evidence to support the use of any one specific treatment (Brooks et al, 2007).

Nevertheless, elements of management indicated by clinical consensus are beginning to receive some support from published research. In particular, there is increasing evidence that an initial clear and unambiguous communication of the diagnosis of PNES and the removal of an erroneous diagnosis of epilepsy is an integral part of management. In itself this may constitute the decisive and only necessary intervention for a minority of patients. (Shen et al, 1990; Farias et al, 2003; Hall-Patch et al, 2010).

Almost 80% of patients with PNES are exposed to Antiepileptic drugs (AED) and about 40% remain on AED after the diagnosis of PNES has been

established (Benbadis, 1999: Reuber et al, 2003; O'sullivan et al, 2007). Consequently, despite the emphasis placed on delivering a clear (un)diagnosis, insufficient attention has been placed on the potential impact that continuing AEDs may have on the prognosis, course or outcome of PNES thereafter.

Studies across a range of physical and psychological disorders have confirmed that such inconsistency between diagnosis and management undermines compliance and outcome (Barski & Borus, 1999). Thus it seems at least plausible that a failure to withdraw AEDs may undermine the diagnosis of PNES and hinder adjustment to the removal of the diagnosis of epilepsy.

Our working hypothesis is that an immediate withdrawal of AEDs following the diagnosis of PNES would enhance the therapeutic effect of a clear delivery of the diagnosis.

In a previous study we showed that AED withdrawal in the context of PNES is safe (Chapter 4). The next step and the aim of the present study was to investigate the potential therapeutic benefit of a planned withdrawal of AEDs following the diagnosis of PNES. We designed a randomised controlled trial comparing changes in attack frequency in patients following differing AED withdrawal regimes. In one group medication was withdrawn immediately after the presentation of the diagnosis of PNES. In a second group, withdrawal of AED was delayed until 9 months after the delivery of the diagnosis. The rationale for this comparison was to observe any possible differences in outcome between the group who had the intervention (AED withdrawal at time of diagnosis) and the control group which continued to take the medication.

5.3. Methods

5.3.1. Aim

The study aim was to investigate the therapeutic effect of a planned withdrawal of antiepileptic drugs in patients with PNES. More specifically, to consider potential benefits of immediate relative to delayed withdrawal, as measured by; reduction in the number of attacks, number of patients that become attack free, changes in physical and psychological health status and healthcare utilisation.

5.3.2. Study design

Pragmatic randomised controlled trial comparing two groups (immediate AED withdrawal (IW) vs. delayed AED withdrawal (DW)) with repeated measures. The study therefore comprises a controlled comparison phase, followed by a replication of the drug withdrawal effect. The design of the study is illustrated in appendix E. The study design adhered to the CONSORT guidelines (Moher et al, 2001; appendix F).

5.3.3. Participants

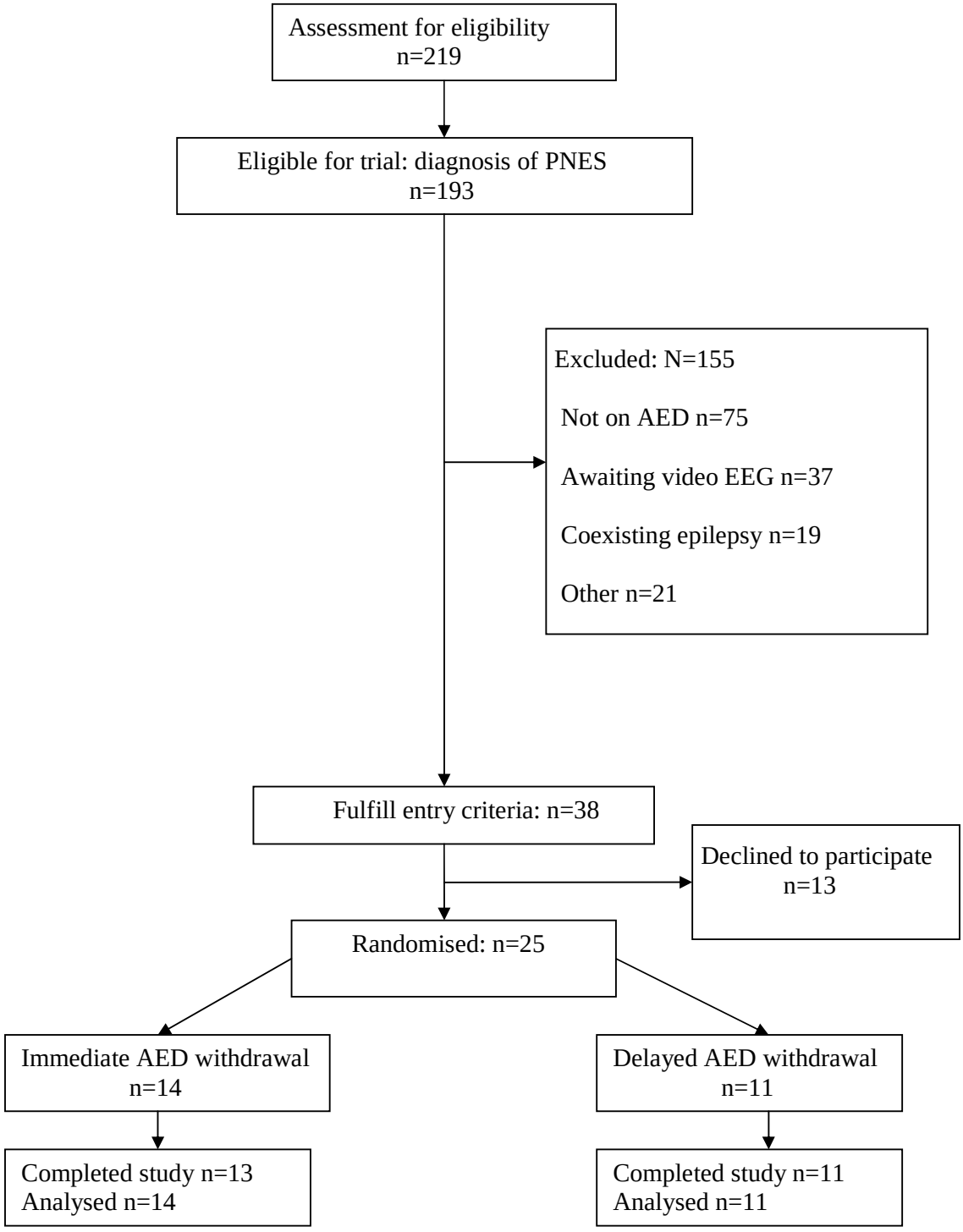
The trial was based at the Glasgow PNES regional clinic in the Institute of Neurological Sciences at the Southern General Hospital. Patients are referred from a wide variety of sources throughout the West of Scotland, including primary and secondary care (total population 2.7 million).

All patients referred to the clinic between April 2001 and January 2004 were screened as potential eligible subjects. Patients were eligible if they had video EEG confirmed diagnosis of PNES, without coexisting epilepsy, and taking at least one AED. Inclusion criteria are shown in table 5.1 and the flow-chart of recruitment is presented in figure 5.1.

Table 5.1: Inclusion criteria for the study.

1	Taking at least one Antiepileptic drug
2	Active NES (> 1 event per month)
3	Diagnosis of NES confirmed by video EEG
4	No evidence of coexisting epilepsy
5	Patient able to give informed consent.
6	Female, if of childbearing age, must not be pregnant and must be using a medically acceptable form of contraception

Figure 5.1: Flow-chart of RCT design.



Emphasis was placed on accurate diagnosis with a strict protocol and a minimum of three clinicians (two epilepsy specialists and a neurophysiologist) were involved, each one assessing the case independently. Details of the diagnostic criteria are shown in appendix G.

5.3.4. Interventions

Subjects were randomly allocated to immediate withdrawal (IW) of antiepileptic drugs or delayed withdrawal (DW). As shown in figure 5.1, patients randomised to IW were asked to immediately start a gradual withdrawal of their AED at the time when the diagnosis of PNES was given. Patients randomised to DW continued to take their medication for a further nine months at which point their medication was slowly withdrawn. The full protocol with details of the intervention is attached in appendix H along with participant consent form (appendix I).

In order to standardize the information given to patients, the research fellow followed the script of a purposely designed semi-structured interview which can be viewed in appendix J. This was based on pilot work described in chapter 4, to elucidate the most frequently asked questions by patients at the clinic following the diagnosis of PNES.

All patients with the confirmed diagnosis of PNES were also given an information leaflet in the form of questions and answers which had also been designed by the author. Further information on the purposely designed patient information sheet can be found in appendix K.

Assessment and data collection took place pre-randomisation (baseline data) and at 9 months post randomisation with subsequent data collection 18 months later at the end of the replication phase. The period of 9 months from the randomisation point was chosen to ensure that all subjects had been off all AEDs for at least two months by the end of the controlled phase.

5.3.5. Drug withdrawal

Medication was gradually withdrawn in weekly decrements following our standard protocol, which had been used regularly at the PNES clinic for a year before the start of the research trial. For patients taking more than one AED, drugs were withdrawn sequentially following our own protocol (appendix D).

5.3.6. Outcomes and data collection

The primary outcome measure was change in self reported attack frequency from baseline to 9 months and at the end of replication phase at 18 months. As well as comparing the absolute reduction of attacks we also analysed data in terms of clinically significant change. Clinical response was defined as reduction of attacks grater than 50%, and remission as being attack free. As secondary outcomes we also measured any changes between and within groups in illness attribution and health care utilisation, as well as differences in physical and psychological health status from baseline to 9 and 18 months.

Patients reported attack frequency retrospectively at each visit since self reporting of attacks in these patients has been shown to be reliable (Quigg et al, 2002). Most patients also used the diary we offered to record the attacks. For secondary outcomes, at all visits, patients completed the same set of questionnaires. All information was recorded in the clinical notes.

The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983; appendix L) was used to assess changes in mood over time. To assess changes related to AED side effects, in particular tiredness (a frequently reported side effect), we used the Side Effects and Life Satisfaction Inventory (SEALS) (Brown & Tomlinson, 1982; Gillham et al, 2000 – see appendix M). Finally the Illness Perception Questionnaire IPQ (Weinman et al, 1996; appendix N) which assesses patients' illness representation was employed. We were particularly interested in assessing changes when on or off medication in their perceived control over their condition.

We recorded basic demographic data for all patients screened for the trial. Progress data for all participants were collected three monthly at the clinic or otherwise through a telephone consultation.

5.3.7. Sample size and power considerations

The only available data on which to base our power calculation were from descriptive retrospective cohort studies. These data suggest that, after diagnosis of PNES, up to one third of the patients become attack free or demonstrate a substantial reduction of attack frequency regardless of management.

Based on the above a power calculation based on an alpha of 0.05 estimated that the sample size required to detect an effect of medium size with 80% power would be 87, reducing to 26 for a large effect (Cohen 1992). Various constraints made it impossible to aspire to anything approaching a sample size of greater that 30 but other steps were taken to maximize power via reducing variance such as imposition of strict entry criteria, the choice of clear and unambiguous end points and maximising treatment fidelity. Despite these manouevres the possibility of inadequate power persisted but it was felt ethically appropriate to proceed with an exploratory trial since there had been no previous controlled trials on management of PNES.

5.3.8. Blinding

Blinding of participants or the clinician was not possible. Due to the nature of the intervention (coming off or remaining on AED), patients had to know in which group they had been allocated. It was the impact of coming off medication or remaining on it, after the diagnosis, that we were interested in assessing, rather than the effects of any AEDs.

The clinician, however, was blinded to adherence with the withdrawing regime which was tested by measuring drug levels in blood. These results were sent to an independent clinician who kept the results confidential until the end of the trial.

Furthermore, the research assistant who administered rating scales at baseline was blind to participant allocation. At the 9 and 18 months visit, patients self-rated the same scales in an attempt to minimise bias and to increase reliability of measures. The scales were scored by the research assistant and results made available to the investigator upon completion of the trial.

5.3.9. Randomisation

A random number list was generated using Excel by an independent clinician who was not involved with the trial. The random list was given to a secretary from another department who again had no knowledge or involvement of the trial. Each time a patient agreed to participate, the nominated secretary was contacted by telephone to obtain a random number. A simple random allocation method was used with patients who were allocated an even number randomised to IW and patients with an allocated odd number randomised to the DW group.

5.3.10. Statistical methods

The evaluation of the data was performed with the computer program SPSS version 14. A descriptive analysis of all data showed that the primary outcome variable (attack frequency) was not normally distributed. Thus within and between group comparisons were made using the appropriate non parametric tests (Wilcoxon Paired Rank Test and Wilcoxon Two Sample respectively). Similarly dichotomous outcomes were compared within and between groups on the appropriate measures (McNemar's test and Fisher's exact test respectively) All analyses were intention to treat, with last observation carried forward used for missing values. A p value $< .05$ was considered statistically significant.

5.4. Results

5.4.1. Sample characteristics at baseline

From April 2001 to Jan 2004 we screened 219 patients of whom 25/219 (11%) were ultimately randomised. Of the excluded patients, 26/219 (11.8 %) had epilepsy only, 79/219 (36%) were not on AED at the time of the study and

13/219 (6%) declined to participate. The remaining 76/219 (35%) of the excluded patients had a clinical diagnosis of PNES and were taking AED, but were excluded because: they did not have video EEG confirmation of diagnosis within the recruitment period (37), had coexisting epilepsy (19) or for other reasons, including pregnancy, inability to consent or history of childhood epilepsy (total 21).

At baseline we had data on the 168/194 patients with PNES who were not included in the study and were able to compare them with the randomised patients as shown in table 5.2 (26/194 of the excluded did not have PNES).

Table 5.2: Comparison at baseline, between randomised patients and the rest of patients with NES not included in the study.

	Excluded n=168	***Randomised n=25***
Female	126/168 (75 %)	20/25 (80 %)
Married	98/168 (58 %)	17/25 (68 %)
Employed or students	38/168 (22 %)	4/25 (16 %)
State benefits	96/168 (57 %)	16/25 (64%)
Reported sexual abuse	43/168 (25.5 %)	8/25 (32 %)
Age at presentation at clinic, Mean	37.6 (sd 14.4)	41 (sd 14.4)
Duration of NES (months), Mean	70.8 (sd 50.8)	57.4 (sd 48.6)
Convulsive attack	114/168 (67 %)	13/25 (52 %)

Following randomisation, the groups assigned to immediate or delayed withdrawal were compared on demographic and clinical characteristics as well as well as factors reported as being of prognostic significance in PNES (Reuber & Elger, 2003). We also rated items identified from our semi structured interview that reflected the impact of PNES in support needs and daily activities (Table 5.3). We found no statistically significant differences between groups.

Table 5.3: Baseline between-groups comparison of possible prognostic factors.

	Immediate withdrawal *N=14*	*Delayed withdrawal* *N=11*
Age in years (mean)	40.7 sd14.1 (16-62)	41.4 sd 15.5 (19-65)
Female(n)	12/14 (85.7%)	8/11(72.7%)
Duration NES in months (mean, range)	59.3 (sd 51.2) (3-144)	59 (sd 47.4) (9-129)
Taking >1 AED	5/14 (35.7%)	6/11(54%)
Attack frequency (median, range)	20(5-720)	12(6-120)
None Compliant with AED	1/14 (7 %)	1/11 (9%)
Daily activity limited by NES	8/14 (57.1%)	5/11 (45.5%)

For the randomised patients, there was no difference in input from a clinical psychologist; four patients (two in each group) declined referral, and the rest were seen by one of the psychologists a mean number of 4 times (IW range 0 to 7 and DW range 0 to 8). Only one patient from the IW group dropped out at four months after initial visit however she was included in the study using the method of last observation carried forward. At the end of the study, one subject from each group (2/25, 8%) was found to have none detectable serum levels of AED suggesting that the group as a whole were concordant with the medication.

5.4.2. Outcome

5.4.2.1. Primary outcome: changes in attack frequency

Our primary outcome was the effect of our intervention (medication withdrawal) on attack frequency at the end of the controlled phase of the study at 9 months from the start of the trial. The control group was in turn exposed to the same intervention at 9 months in a subsequent replication phase with patients being followed up for 18 months in all.

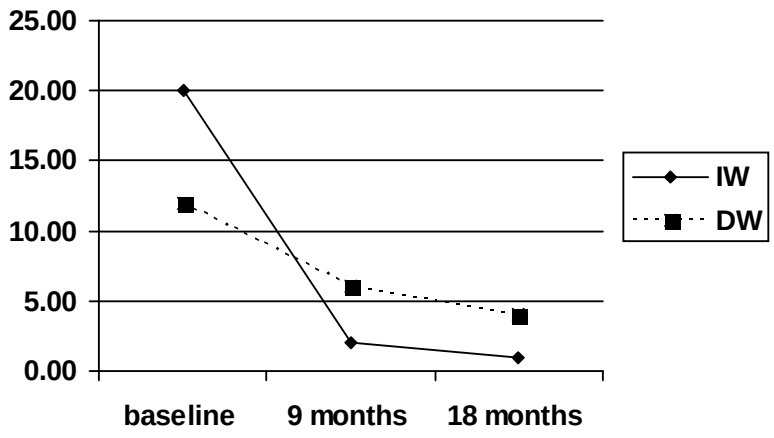
At baseline all patients (n=25) reported monthly attacks ranging between 10 and 295; the data were not normally distributed. As a result, and considering the

small size of our sample, we used the median values to compare groups as a more stable way to illustrate the group central tendency.

At baseline the median of attacks of the IW group was 20(range 5-720) compared with a median of 12 (range 6-120) for the DW group, this difference was not statistically significant (p=.700).

As can be seen in figure 5.2, median number of attacks declined across the study in both groups. At the end of the controlled phase the IW group reported a median attack frequency of 2(0-295) compared with 6 (0-100) for the DW which, when compared, was not a statistically significant. By the end of the replication phase the medians had reduced further in both groups to a median of 1(0-6) in the IW group and of 4(0-32) in the DW group, which again when compared was not statistically significant. It is noteworthy that in both groups of theses values had reduced considerably.

Figure 5.2: Changes in median number of attacks between IW and DW groups at main end points.



Visual inspection of figure 5.2 suggests that subjects in the IW group had a greater reduction from baseline than the DW group at the end of the controlled phase. Using within group change scores for comparison of median values the reduction for the IW group was statistically significant (p=.028) and that was not the case for the DW group.

5.4.2.2. Clinically significant changes between groups

To assess the clinical impact of our intervention we compared both groups for the proportion of patients attack free and the proportion with >50% reduction of attacks as well as differences in health care utilisation as shown in table 5.4.

Table 5.4: Clinical and social outcomes between groups from baseline to end of the study (*P<.05)

	Baseline	**9 months**	**18 months**
	IW DW	IW DW	IW DW
Attack frequency (median and range)	20 (5-720) 12 (6-12)	2 (0-295) 6 (0-100)	1 (0-60) 4 (0-32)
Attack free	0/14 0/11	3/14(21%) 3/11(23%)	7/14(50%) 3/11(27%)
Use of emergency medication	6/14(43%) 4/11(36%)	0/14* 4/11(36%)	0/14 0/11
Use of emergency services for NES	3/14(21%) 5/11(45%)	1/14(7%) 3/11(23%)	0/14 0/11
Use of emergency services for other than NES	10/14 (71%) 8/11(2%)	4/14(28%) 4/11(36%)	0/14 0/11
Working	2/14(14%) 0/11	2/14(12%) 0/11	4/14*(28%) 0/11
Receiving state benefits	11/14(78%) 10/11(91%)	11/14(78%) 10/11(91%)	9/14 (64%) 8/11 (72%)

Inspection of the data in figure 5.3 (below) shows a sustained increase in the number of patients achieving >50% reduction of attacks throughout the study. This improvement continues beyond the controlled phase, and is particularly noticeable in the IW group by the end of the study, although this difference is not statistically significant (p=.700). As shown in figure 5.4 at the end of the controlled phase (9months) both groups had a similar proportion (IW 21% vs DW 27%) of patients who had achieved full remission status for at least two months. Interestingly, at the end of the extension phase, the number participant numbers had doubled under IW (50%), suggesting some enhanced effect in the longer term that was not evident in DW (27%) at that time point. Formal analysis, however, did not support this visual impression (p= .076).

Figure 5.3: Changes in percentage of patients with > 50% reduction of attacks between IW and DW group at main end points.

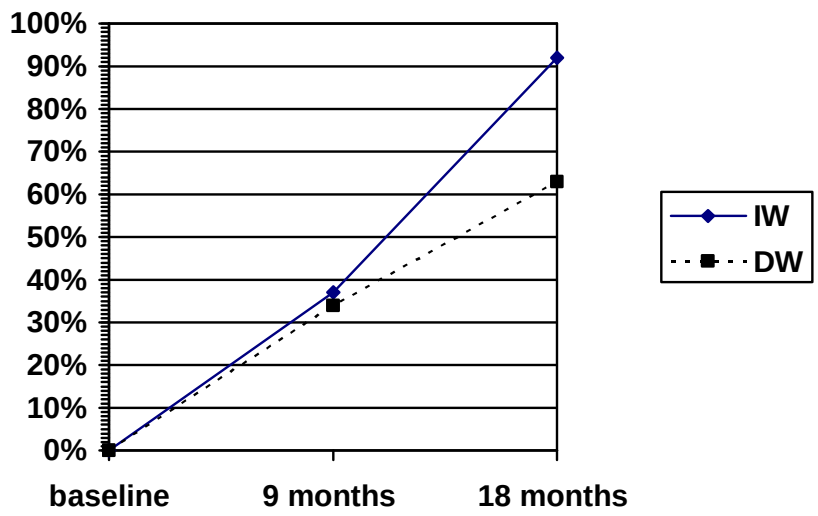
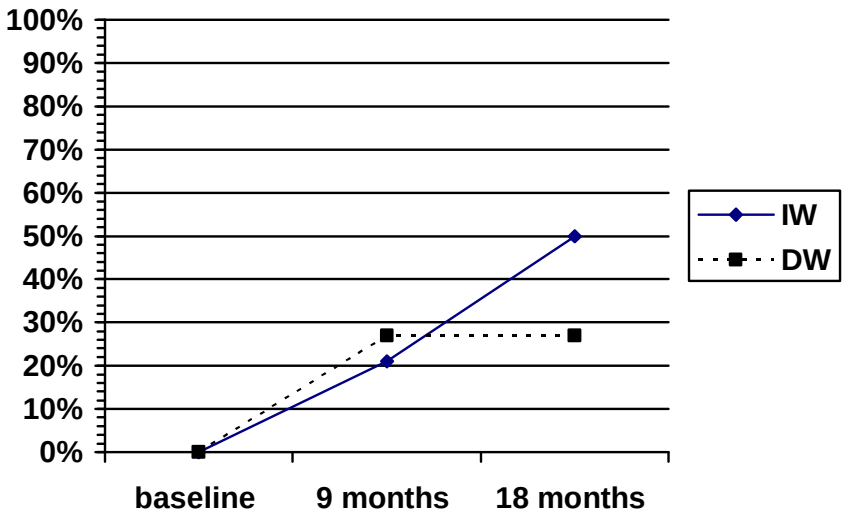


Figure 5.4: Changes in percentage of attack free patients between IW and DW group at main end points.



In terms of health care utilisation, at baseline a similar proportion of patients in both groups received antiepileptic emergency medication to control their attacks, at 9 months however no patients from the IW group were using emergency medication compared with 4/11(36%) patients in the DW group,

representing a statistically significant difference (p=0.026). This effect disappeared by the end of the replication phase when all patients were off AEDs and no patient in either group was receiving antiepileptic emergency medication.

A similar pattern of improvement was observed in the use of emergency services due to PNES related symptoms, although in this case the difference between groups at 9 months was not statistically significant. By the end of the replication phase again no patients were using emergency services because of their attacks.

The use of health care services for other chronic symptoms remained stable throughout the study in both groups. Only a small percentage of patients (IW: 3/14 -21%, DW; 2/11-18%) presented to medical services with new symptoms arising since the start of the trial at 9 months, by the end of the study, however, no use of medical services for new symptoms were reported in either group.

5.4.2.3. Psychosocial outcomes

In terms of social outcomes, little change was noted in either group by the end of the controlled phase. At the end of the replication phase, the number of subjects receiving state benefits and the reported level of disability due to PNES were reduced in both groups. We observed a change in working status for the IW group (4/14, 28%) at the end of the study, which was significantly greater than the DW group where no patients were employed.

From the psychological rating scales, the HADS mean scores for anxiety were at the lower end of mild (>10) in both groups at baseline and remained at the same level throughout the study (see table 5.5)

Table 5.5: HADS scores over the three assessment points, between groups.

	Baseline		9 months		18 months	
	IW	DW	IW	DW	IW	DW
Anxiety						
Mean -SD	10.9	9.9	8.7	8.1	10.0	9.5
	(6.4)	(3.4)	(4.4)	(4.3)	(3.2)	(3.4)
Depression						
Mean –SD	9.0	6.2	6.2	7.5	6.9	7.0
	(5.5)	(4.0)	(4.8)	(3.5)	(3.5)	(3.8)

The mean scores for depression appear to improve for the IW group by the end of the control phase as opposed of the DW group were the score increased slightly, however this was not statistically significant.

As shown in table 5.6, the only statistically significant difference detected on the SEALS questionnaire, was the significantly higher number of patients from the DW at the end of the controlled phase (who were still on medication) complaining of tiredness. By the end of the replication phase (18 months), when all patients were off AEDs, the scores in the DW group were lower and not significantly different from the IW group. For the rest of the domains there were no significant differences between the two groups throughout the study.

Table 5.6: SEALS scores for the three assessment points, between groups.

	Baseline		9 months		18 months	
	IW	DW	IW	DW	IW	DW
Worry	8	7.9	7.7	6.3	8	7.6
(Mean-SD)	(2.8)	(4.9)	(2.4)	(3.5)	(2.5)	(2.6)
Cognition	25.8	24.9	24.2	31.2	26.3	26.8
(Mean-SD)	(12.6)	(11)	(12.1)	(7.6)	(12)	(12.9)
Temper	7	6	7.2	6.4	6.6	6.2
(Mean-SD)	(3.7)	(3.1)	(3)	(3.3)	(3.5)	(3.2)
Tiredness	7.6	9.2	7.1 *	10.6	9.2	8.2
(Mean-SD)	(3.9)	(4.7)	(4.1)	(3.8)	(3.5)	(4.7)
Dysphoria	9.5	10.9	8.7	9.4	11.3	11.4
(Mean-SD)	(5.2)	(3.3)	(4.7)	(4)	(3.8)	(3.2)

*P<0.05

As illustrated in Table 5.7, the domains from the IPQ that reflected an internal locus of control (attacks caused by; stress, state of mind, own behaviour) increased in both groups throughout the study, this increase was statistically significant for the IW group by the end of the replication phase, where more subjects were attributing their attacks to their mental state (p=0.005). At that, point, a higher proportion of subjects in the IW group which had been off medication for 18 months were also attack free. For the remaining domains of the IPQ there were no statistically significant differences between groups.

Table 5.7: IPQ scores for the three assessment points, between groups.

	Baseline		9 months		18 months	
	IW	DW	IW	DW	IW	DW
Number of symptoms	8.3(2.2)	7.3(2.5)	7.4(4.3)	8(2.4)	6.6(4.2)	5.2(3.5)
External locus of control	14.6(5.6)	16.3(4.7)	14.4(4.5)	14.7(4.4)	14,3(4.9)	14.4(3.6)
Internal locus of control	8(3.4)	8(2.6)	10(2.4)	9(3.4)	11.2(1.8)	8.3(2.8)
Control cure	3(0.4)	3(0.2)	3.1(0.7)	3.2(0.6)	2.5(0.8)	2.7(0.3)
Consequence	3.8(0.7)	3.3(0.8)	3.4(6.5)	3.4(6.0)	3.3(0.7)	3.2(1)
Time line	3.1(0.4)	3(0.5)	2.7(0.5)	3(0.3)	3.4(0.8)	3.2(0.7)

5.5. Discussion

This is the first controlled trial aimed at determining the possible therapeutic effect of scheduled AED withdrawal at the time of diagnosis of PNES (Bodde et al, 2009). Our hypothesis was that immediate AED withdrawal would enhance the therapeutic benefit of clear and unambiguous delivery of the diagnosis.

Our hypothesis was partially confirmed by statistical differences between the pattern and extent of reduction in attack frequency in the IW group relative to the control group. These effects however, have to be seen in the context of overall benefit in giving the diagnosis clearly in the first place.

A tentative suggestion could be made that the co-delivery of the diagnosis and medication withdrawal resulted in a statistically significant and persistent fall in

attack frequency manifested over the course of the study as compared to the group where the interventions were delivered separately.

Clinical improvement throughout the study was observed and by 18 months all but one of the patients in the IW group had a >50% reduction and half were attack free which represents a good outcome when compared with current literature (29%-52%) including a pilot study evaluating the impact of Cognitive Behaviour Therapy as a treatment for PNES (Ettinger et al, 1999b; Reuber et al, 2003a; Goldstein et al, 2004)

Our other clinical outcome measures provide some clearer suggestion of an effect of AED withdrawal following the delivery of the diagnosis of PNES. The use of emergency services for PNES dropped to zero in the IW and DW group, as did the use of emergency AEDs; this change was noted earlier in the IW group and in the case of use of emergency AED, the difference between groups was significant. This is consistent with our previous study which also showed a drop in use of emergency services following the diagnosis and AED withdrawal which was also independent of continuation of the attack disorder (McKenzie et al, 2009).

This reduction in demand for emergency healthcare suggests a change in attitude of the attacks themselves, on the part of carers if not patients. A possible explanation could be that the withdrawal of medication has the effect of discouraging ‘medicalisation’ of symptoms. Another important point is the potentially detrimental effect of health care contacts in this group of patients (Barsky & Borus, 1999). A reduction of contacts may therefore be beneficial in the long term; however this issue requires further study.

There exists a concern that patients who cease have will go on to develop new somatic complaints. Our data are reassuring in this regard since only a minority of patients in each group presented with new symptoms, all of which had resolved buy the end of the study.

Occupational status is poor in patients with PNES, and existing evidence suggests it remains so even in patients whose attacks cease to be dependent

(Quigg et al, 2002; Reuber et al, 2003a) and our relatively short-term data is consistent with this.

At the start of the study all our patients were taking AEDs which are known to have mood stabilising effects and are routinely used to treat emotional dysregulation and affective disorders (LaFrance, 2007). One possible outcome of the AED withdrawal would therefore be exacerbation of anxiety and depression. The HADS scores however remained stable for both groups throughout the study.

As might be expected the SEALS tiredness scores at 9 months were significantly higher for the DW patients who were still on medication. This finding is an example of the negative impact that medication has in these patients.

One of the hypotheses behind the study was that removing medication would enhance the message that PNES are not a result of a neurological condition and change patients illness attributions. Patients' perception that the cause of their attacks was due to stress increased steadily in the IW group becoming significantly higher at the end of the study, reflecting a greater internal locus of control. For the rest of the IPQ results, it is difficult to draw conclusions because of the potential for multiple testing effects. Importantly none of the small changes in scores throughout the study reflected deterioration.

5.5.1. Methodological considerations

This study was conceived as an exploratory trial which could inform future research in a field lacking in evidenced-based treatments and we are therefore aware of the limitations of the study, particularly our small sample size (n=25). This was on the other hand a pragmatic trial conducted within a busy regional epilepsy service which potentially makes our experience and results relevant to other epilepsy units.

Despite a high patient through-put, our difficulty in recruiting participants can be partly explained by the fact that our inclusion criteria were very strict; however

we deemed the robustness of the diagnosis of PNES essential in terms of the validity of the study.

Retention was on the other hand very high, possibly reflecting the effort of the investigators to keep as many patients as possible by using a proactive and flexible approach regarding appointments. There is no doubt that from that point of view all our subjects received a great deal of attention which may have influenced the outcome, particularly in a group of patients that often feels rejected and misunderstood by physicians (Mokleby et al, 2002; Carton et al, 2007)

The fact that the groups were small was problematic, particularly considering that we were testing the effect of a single intervention in a group of complex and heterogeneous patients (Lesser et al, 2003; Cragar et al, 2005; Baslet et al, 2010). We tried to minimize this variability by comparing our groups at baseline not only on demographic data but also other factors which had shown to influence the outcome of patients with PNES in previous observational studies and in all these aspects both groups were very similar.

An important factor to consider in terms of the effect of our main intervention is that in our daily practice, we positively emphasise and explain the importance of withdrawing medication to all patients as a crucial step to a complete recovery. In order to assess the impact of this intervention and to randomise and consent patients we had to be neutral when discussing the effects of medication withdrawal, therefore diluting the message of the importance of coming off AED and possibly reducing impact of the intervention.

Recruitment and retention, the heterogeneity of the patients, controlling for Hawthorne effects and choice of adequate outcome measures were all methodological issues we encountered. Reassuringly, La France et al., in their report of their pilot study for a treatment trial of PNES, describe very similar difficulties and make some recommendations for the success of future research (LaFrance et al, 2007).

5.5.2. Ethical considerations

The ethical implications of leaving subjects with NES on AEDs for 9 months after the diagnosis, was discussed extensively by the team. We were clear in the fact that our study was designed to compare two pragmatic management alternatives and although it is our feeling that patients with PNES should not be maintained on AEDs, in practice they often are to the point that it constitutes treatment as usual for many physicians (Reuber et al, 2003b; O'sullivan et al, 2007; Hall-Patch et al, 2010).

5.6. Conclusions

Our research represents a methodologically rigorous attempt to evaluate an intervention on the management of these very complex patients and represents an important contribution to the very few studies designed to test a specific management strategy for PNES.

The present study may be regarded as an exploratory exercise and as such has provided a suggestion that withdrawing AED enhances the effect of a clear delivery of the diagnosis. This effect is reflected in a persistent reduction in attack frequency and a cessation of the use of emergency services and medication following AED withdrawal. Importantly, none of our data show any negative effects.

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Chapter 6:

Psychosocial outcomes of patients with psychogenic nonepileptic seizures 18 months after diagnosis

6.1. Abstract

Background: Psychogenic nonepileptic seizures (PNES) are psychologically mediated attacks that resemble and are often mistaken for epilepsy. The evidence base regarding the management of PNES is limited; however, clinical consensus increasingly supports a clear communication of the diagnosis followed by medication withdrawal as the first management step.

Aims: To assess the longer term psychosocial outcomes of AED's withdrawal in a group of patients with PNES.

Methods: The current study is an observational extension of a pragmatic randomised trial comparing the clinical outcomes of PNES patients randomised to immediate (IW) versus delayed withdrawal (DW) of AED following the diagnosis. Comprehensive psychosocial data for the whole sample was collected at baseline and 18 months latter when all subjects were off AED'S

Results: We found significant changes in illness perception with a reduction in reported symptoms, a shift towards a more internal locus of control and fewer patients reporting a chronic view of PNES. Patients' mood also improved with significantly lower depression scores at the end of the study. For the social outcomes we detected a significant improvement in self reported level of functioning as well as an almost significant reduction of patients receiving state benefits because of PNES only. Employment status did not change from baseline.

Conclusion: A clear delivery of the diagnosis of PNES followed by AED withdrawal is successful in removing the label of epilepsy, helping patients to shift towards a more psychologically based explanation without negative effects on their psychosocial status.

6.2. Introduction

Psychogenic non epileptic seizures (PNES) are paroxysmal events that resemble or are mistakenly ascribed to epilepsy, without being associated with epileptiform discharges in the brain. Non epileptic attacks are relatively common and represent a significant part of the workload of epilepsy specialists and other physicians (Martin et al., 1998). An underlying psychological process is often assumed but whether causal or not, patients presenting with PNES certainly do describe high levels of associated psychopathology, with depression and anxiety being most frequently reported (Bowman & Markand, 1996; Moore & Baker, 1997; Mokleby et al., 2002; Bailles et al, 2004; D'Alessio et al, 2006). Their experience of disability, unemployment and receipt of benefits is just as high as in patients with epilepsy (Szaflarski et al, 2003; Hixson et al, 2006).

The purpose of this study is to present the 18 month outcome of a consecutively and prospectively recruited series of patients with a video EEG confirmed diagnosis of PNES, and who underwent a planned withdrawal of medication and subsequent brief psychological therapy.

6.2.1. Background and rationale for this paper

Increasing awareness of the diagnosis of PNES and the introduction and subsequent wide availability of simultaneous video EEG has substantially improved the accuracy of diagnosis and the differentiation between PNES and epilepsy (Cragar et al, 2002). The same cannot be said for prognosis and management (LaFrance & Devinsky, 2004). Most available treatment studies are methodologically poor, and difficult to interpret, and give little support to a single overarching rationale or approach. However, one area of growing consensus within the literature is the acceptance that the initial step of communicating the diagnosis effectively can in and of itself have substantial therapeutic efficacy. Communicating the diagnosis in a clear and unambiguous way has been shown to help patients understand and ultimately accept the diagnosis, an essential prerequisite of future engagement with any potential therapeutic intervention, whatever its form and rationale (Shen et al, 1990;

Farias et al, 2003; Hall-Patch et al, 2010)..

Most patients with PNES are originally diagnosed as having epilepsy and treated with AED. AEDs have deleterious effects on physical health and psychological well-being and their inappropriate prescription courts substantial iatrogenic harm (Niedermeyer et al., 1970; Howell et al., 1989; DeToledo et al., 2000; Peruca & Meador, 2005). Over and above this, however, the fact of being prescribed AED may amplify and reinforce illness perceptions towards 'organicity' and attenuate and undermine the message that NES is a 'non-organic' disorder, perhaps militating against the patient's engagement with behavioural or cognitive treatments designed to help them gain insight into or control their attacks (Jacoby et al., 1992; Carton et al., 2003). Observational work (Reuber & Elger, 2003c) suggested an association between remaining on anticonvulsants post diagnosis of PNES and a poor prognosis and the RCT described in the previous chapter confirms the specific efficacy of diagnosis and medication and medication withdrawal as an intervention in PNES.

Although attack reduction or cessation is the goal of treatment, there is a lack of consensus as to what might constitute a good outcome. Although reduction or cessation of attacks has obvious face validity and is easily and reliably rated as a measure of the 'disorder', it may not translate into or correlate with broader psychosocial recovery (Quigg et al, 2002; Reuber et al, 2005).

Studies of PNES have been criticised for their over narrow concentration on seizure frequency as an endpoint (Reuber et al., 2005; LaFrance et al., 2008). There is also evidence from studies looking at recovery beyond reduced seizure frequency that report ongoing psychological morbidity and poor social functioning even when a significant proportion of patients report a reduction or cessation of attacks. (Quigg et al, 2002; Reuber & Elger, 2003c; McKenzie et al, 2009).

In summary, the evidence-base regarding the management and outcome of PNES is limited, but the converging imperatives of good practice and clinical consensus regarding the clear communication of the diagnosis and early withdrawal of medication, are beginning to find a level of support in observational studies (Shen, 1990; Farias, 2003; Thompson, 2005; Hall-Patch

et al., 2010) as well as the experimental work described elsewhere in this thesis.

Following on from the RCT described in chapter 5 the purpose of this paper is to present the longer term psychosocial outcomes in 24 prospectively recruited patients with PNES following their exposure to a consistent and thorough diagnostic assessment and management strategy.

6.2.2. Aims of the study

To assess the longer term psychosocial outcomes of AED's withdrawal in a group of patients with PNES.

6.2.3. Research questions

Are there any significant changes in patient's mood following AED withdrawal?

Are there any significant changes in patients well-being following AED withdrawal?

Are there any significant changes in patient's attribution and representation of PNES following the withdrawal of AED's?

6.3. Methodology

The current study is an observational extension of a pragmatic randomised trial comparing the clinical outcomes of PNES patients randomised to immediate (IW) versus delayed withdrawal (DW) of AED following the diagnosis of PNES. Delayed withdrawal took place at 9 months following diagnosis. The current study presents a cohort comprising the subjects from both arms when all patients had been off medication for at least 6 months following the gradual withdrawal of AED's.

The trial was based at the Glasgow PNES clinic in the Institute of Neurological Sciences at the Southern General Hospital between April 2001 and December 2003. Patients are referred from a wide variety of sources throughout the West

of Scotland (total population 2.7 million). Full details of the research protocol can be found in appendix H.

6.3.1. Management (intervention)

The diagnosis of PNES was confirmed by video EEG and explained in a clear and supportive manner, this was backed up with written information to ensure that all the same points were covered (see appendix J for scripts of the visits and patient information).

As detailed in chapter 5, all patients were seen 3 monthly to monitor medication withdrawal and assess progress. In terms of psychological intervention, following the diagnosis, all subjects were given the option to attend a clinical psychologist for up to 6 sessions of a Cognitive Behaviour Therapy based intervention.

All participants were offered an appointment with one of the two psychologists of our service; the referrals were allocated alternatively to psychologist A or B. All subjects were seen within four weeks of referral and had at least two visits during the first 9 months of the study.

The team psychologists delivered a cognitive behaviour therapy (CBT) based treatment, with an initial session focusing on the acceptance and understanding of the diagnosis, subsequent sessions dedicated to identifying triggers for the attacks, possible stressors and relaxation training with a final session to review the therapeutic intervention and discuss relapse prevention techniques. Because of the limited availability of clinical psychologists subjects were offered a minimum of 2 fortnightly sessions and a maximum of 6.

At the start of the study all patients were on AED medication since this was one of the inclusion criteria and by 18 months all participants had been gradually withdrawn as part of the management plan.

6.3.2. Measures

This paper focused on; psychological and general health outcomes as measured by the IPQ, HADS and SEALS, and social and occupational status and adjustment as indicated by proxy measures such as employment, receipt of benefits and perceived functional status. Because of time and personnel constraints all scales were self reported.

Clinical outcomes as attack frequency, as measured by a diary and health care utilisation are reported in detail in Chapter 5.

All scales were completed at baseline, 3 monthly follow up and upon study completion, scored by a research assistant and the results concealed from the primary researcher and those involved in administering psychological treatment until the end of the study.

The scales were as follows:

6.3.2.1. Seizure diary

To record attack frequency subjects were given a standardised diary designed specifically for the study. The reason for creating our own attack diary was to ensure that it contained no reference to epilepsy or epileptic seizures which could potentially send mixed messages and affect patient's view of the attack disorder. The diary was completed based on self report and carer and relative comment (see appendix O).

6.3.2.2. National Adult Reading Test (NART-2nd edition)

A list of 50 irregularly spelled words is read aloud by participants, and scored for pronunciation errors to determine a predicted full scale IQ. Subjects with a score lower than 70 were not included.

An IQ within the normal limits was one of the inclusion criteria for the trial. As well as ensuring that all subjects had the capacity to understand there is also evidence that patients with a low IQ have a distinct underlying mechanism for PNES (Duncan et al, 2008).

6.3.2.3. Side Effects and life satisfaction inventory (SEALS; Brown & Tomlinson, 1982)

This inventory is a 50 item self reported questionnaire derived from, designed for, and validated in subjects with epilepsy which is sensitive to change over time. In general terms it corresponds to a measure of well being and physical and psychological health with particular reference to the day to day problems and drug side effects reported by patients with epilepsy. The scale was derived from symptoms and side effects reported by patients, with principal component analysis identifing five main areas of difficulty; “cognition” ,”dysphoria” ,”temper”, “tiredness” and “worry”. Each subscale contains a series of positively and negatively phrased items with a four point response matrix between 0 and 3 with 0 being “never” and 3 “many times”.

The SEALS inventory has been found to have the qualities of validity, reliability and responsiveness to be used in research and clinical settings. The scale has a good internal consistency with a Cronbach’s coefficient >0.7 for all subscales. It is a valid tool to investigate and monitor the effect of AED therapy on quality of life and to measure changes in patient’s well-being in response to changes in management (Gillham et al, 2000).

This scale, although originally designed for patients with epilepsy, seemed the most appropriate tool to assess potential changes following the withdrawal of AED as part of the management of PNES.

6.3.2.4. Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983).

The HADS was developed to identify possible cases of anxiety and depression amongst patients in non-psychiatric hospital clinics and to monitor mood changes over time. To avoid confounding by physical illness, the symptoms of anxiety and depression relating to physical illness were excluded from the questionnaire. The HADS is a self-report scale comprising of 14 items that probe aspects of depression and anxiety in the past 7 days. The scale can be divided into two subscales (anxiety and depression), with higher sum scores

indicating more anxiety and depression. Scores <8 indicate the normal range, scores between 8 and 10 reflect mild symptoms and scores >11 indicate clinically relevant symptoms. The scale has a sensitivity of 83.3% and specificity of 61.5% for identification of psychiatric cases. The HADS has similar screening properties when compared with more comprehensive instruments used to identify anxiety and depression (Bjelland, 2002).

6.3.2.5. Illness Perception Questionnaire (Weinman et al 1996)

This provides a quantitative assessment of the five components of illness representation derived from Leventahl's Self-Regulatory Model. The model proposes that symptoms generate and are interpreted and acted upon via an overarching cognitive and emotional representation of the illness. The scale is divided into 5 subscales:

- Identity: the label the person uses to describe the illness and symptoms they view as being part of the disease.
- Consequences: the expected effects and outcome of the illness.
- Cause: the patient's idea about the cause of their illness.
- Time-line: patient perception of how long the illness will last.
- Control: the extent to which the person will recover or control the illness.

The first subscale is Illness identity and comprises 12 core symptoms that patients rate for frequency on a four point scale, ranging from all the time to never. The cause subscale can be subdivided into attribution to external factors (germ or virus, pollution, hereditary factors, poor medical care and chance) and internal factors (stress, my state of mind, own behaviour, other people had a role).The other three subscales included a series of statements related to time line, consequences or control. The individual items are scored on a 1-5 scale indicating the strength of the agreement with the individual statement with higher scores indicating stronger agreement. An average score of the individual items is obtained.

For the time-line subscale, higher scores represent beliefs that the illness will last a long time, higher scores on the consequence subscale reflect a belief of

greater consequences and, finally, higher scores for the control-cure subscale reflects patients' impression of lack of control.

This early version of the IPQ has been found to have a good re-test reliability and internal consistency (Cronbach's Alpha >0.7) as well as discriminant and predictive validity (Weinman & Petrie, 1997).

6.3.3. Statistical analysis

The evaluation of the data was performed with the computer program SPSS for Windows version 14.

A descriptive analysis of the data for continuous variables (i.e. IPQ, HADS and SEALS) showed that the results were essentially normally distributed (as assessed by kurtosis and skewedness, with both metrics lying between -1 and +1), paired t-tests were therefore used throughout. Sensitivity analysis via equivalent non parametric tests did not significantly alter the results. To maximise ecological validity social functioning data was captured as a series of real world dichotomous outcomes such as employed vs. unemployed, analysed using McNemar's test. Finally a post hoc analysis was conducted for all outcomes for the grouping / predictor variable of attack freedom, using independent t tests or Fishers test as appropriate to assess for any difference in baseline or outcome for those subjects demonstrating attack freedom.

For all statistical analyses a p value <.05 was considered statistically significant. Outcome data were also presented after correcting for multiple testing using the Bonferroni correction.

One of the patients (1/25, 4%) randomised to immediate withdrawal was lost to follow up after the second control visit; all their data has been excluded from analysis subsequent to this point.

6.4. Results

6.4.1. Demographics and baseline characteristics

The mean age of the subjects at presentation to the clinic was 41 years (sd 14.4), ranging from 16 to 65. The majority of patients were female (20/25, 80%) and 17 /25 (68%) had a partner or were married. All patients were on medication as it was one of the entry criteria with a median number of AED of 1 ranging between 1 and a maximum of 3.

The mean IQ as estimated by the NART was 99.6(sd 8.4), ranging between 80 and 115. At baseline, 14/25(56%) patients had previous contact with psychiatric services and 8/25(32%) were prescribed an antidepressant. Five out of the twenty five patients (20%) had previously attracted a diagnosis of personality disorder, 7/25 (28%) reported other chronic physical symptoms, and 8/25(32%) disclosed a history of sexual abuse.

In terms of the psychotherapeutic intervention, 4/25(16%) subjects declined to see a psychologist and the rest had a median of 3.8 sessions (range 1-8). At the end of the study 4/10 of the attack-free patients and 5/14 had managed to complete the 6 sessions, this was not statistically significant (McNemar test p=0.26).

At baseline the median attack frequency was 20 per month (range 5- 700); as compared to 2 per month (range 0- 60) at the end by which time 10/24 (41.6%) patients had been attack free for at least 2 months. Following drug withdrawal no patient was in contact with the emergency services or had received acute anticonvulsant treatment, a significant reduction of healthcare utilisation compared with baseline ($p< 0.002$).

One of the patients (1/25, 4%) randomised to immediate withdrawal was lost to follow up after the second control visit, all their data has been excluded from analysis subsequent to this point.

6.4.2. Psychological outcomes

As shown in Table 6.1, the mean scores for anxiety and depression at baseline were within the mild range. There were no significant differences between the HADS scores of the 8 patients on Antidepressants and the rest of the sample at baseline. By the end of the study the mean score for depression had decreased significantly (p=0.05) with a mean within the normal range.

Table 6.1: Comparison of the mean(sd) scores on psychological outcome measures between baseline and end of the study at 18 months.

	At presentation	**At 18 months**	
	Mean (sd)	**Mean (sd)**	***p* - value**
HADS			
Anxiety	10.5 (5.3)	9.8 (3.2)	0.5
Depression	8.5 (4.9)	6.7 (3.5)	0.05
SEALS			
Worry	7.7 (3.9)	6.7 (2.5)	0.89
Temper	6.6 (3.4)	6.8 (3.1)	0.67
Cognition	24.9 (11.7)	26.5 (3.5)	0.68
Tiredness	8.3 (4.09)	8.6 (4.3)	0.66
Dysphoria	10.1 (4.5)	9 (4.3)	0.25
IPQ			
Number of reported symptoms	7.8 (2.4)	5.9 (3.9)	0.03*
External locus of control	15.4 (5.2)	14.4 (4.3)	0.4
Internal locus of control	8 (3)	10 (2.7)	0.01*
Time line	3 (0.3)	2.6 (0.6)	0.01*
Consequences	3.5 (0.8)	3.2 (0.8)	0.14
Control	3 (0.5)	3.3 (0.8)	0.15

Paired T test ,* P< 0.05

Despite withdrawal of medication we did not detect any significant changes in the SEALS scores between baseline and the end of the study.

As shown in Table 6.1, the IPQ scores significantly decreased from baseline for several domains; at 18 months there was a significant reduction in number of symptoms reported, measures reflecting a higher internal locus of control had improved and patients were less likely to perceive their disorder as chronic.

6.4.3. Social outcomes

At baseline 3/25 (8%) subjects were working or in full time education and 22/25(88%) were unemployed and on disability benefits (see table 6.2).

Table 6.2: Comparison of social functioning outcome data from baseline to end of the study at 18 months.

	At baseline	At follow up	p
Employment status: Working	2/25(8%)	4/24(16%)	0.50
On social security benefit			
No	4/25(16%)	8/24 (33%)	0.25
Yes for NES	7/25(28%)	2/24 (8%)	0.06
Yes for other	14/25(56%)	15/24 (56%)	0.22
Able to attend clinic alone	5/25 (20%)	10/24 (40%)	0.18
Level of activity			
Premorbid level	0/25	8/24 (32%)	0.008*#
Limited by NES	13/25(52%)	7/24 (28%)	0.22
Limited by other	12/25 (48%)	10/24 (40%)	0.62

McNemar test ,* P<0.05
remained sig. after Bonferroni correction

In terms of previous occupation, most patients had unskilled jobs (14/25, 56%) and 3 patients had never worked. Interestingly 5/25 (20%) patients had jobs in social care, four as care assistants and one as a nursery nurse. At 18 months, three patients moved on to further education; one subject started a psychology degree and the other two a nursing a degree. One patient had stopped working; however, 3 had managed to get back to employment by the end of the study.

Seven patients in the study were awarded benefits only because of the attacks and based on an initial diagnosis of epilepsy. At the end of the study, only two of these 7 patients were still receiving benefits, this reduction showing a trend towards significance (p = 0.06). As shown in table 6.2, measures of dependence also improved with twice as many people able to attend the clinic alone and a

significant higher number of subjects reporting levels of daily activity back to a pre morbid level.

6.4.4. Post-hoc analysis of attack free patients

At outcome, and as presented in table 6.3, subjects who were attack free were compared with the remainder on psychosocial outcome to investigate any relationship between attack freedom and broader measures of recovery.

Table 6.3: Post-hoc analyses comparing attack or not attack free patients with all outcomes which significantly changed from baseline .

	Attack Free patients	Non-Attack Free	p-value
Depression scores (HADS), Mean (sd)	4.9(2.9)	5.6(2.1)	0.01*
Number of reported symptoms (IPQ), Mean (sd)	4.2(4.1)	7.2(3.4)	0.05*
NES seen as chronic, Mean (sd)	2.2(0.6)	2.9(0.4)	0.03*
Internal locus of control (IPQ), Mean (sd)	9.4(2.8)	10.8(2.4)	0.23
Attribution to stress, Mean (sd)	2.4(1)	2.9(1.1)	0.35
Pre-morbid level of activity	1/24(%)	7/24(%)	0.01*
On benefits because of NES only	2/24(%)	0/24(%)	0.58

Patients in the attack free group had lower scores of depression as assessed by the HADS questionnaire; were reporting lower number of symptoms; and were less likely to regard their condition as chronic. There were no differences between groups in terms of locus of control.

In terms of the social outcomes, attack free patients were more likely to report activity at a pre-morbid level but there were no significant changes for receiving benefits because of PNES. Only a small number of patients had been on benefits purely because of PNES, and although this number clearly fell in absolute terms there was insufficient power to demonstrate this statistically.

6.5. Discussion

These results are encouraging because they show a significant improvement from baseline on a number of psychological and social functioning measures.

However, when looking at these results, in the context of the 40% of attack free patients 18 months after the diagnosis, these changes appear modest.

Our results are in line with other outcome studies reporting limited improvement of social functioning variables at follow-up (Quigg et al, 2001; Reuber et al, 2005; Kuyk et al, 2008). Poor social outcomes have also been reported in other medically unexplained symptoms (Stone et al, 2003; Sharp et al, 2010).

We found significant changes in illness perception with a reduction in reported symptoms, and a shift towards a more internal locus of control as well as significantly lower depression scores at the end of the study. For the social outcomes we found a significant improvement on a self reported level of functioning, as well as an almost significant reduction of patient receiving state benefits because of NES only. Employment status on the other hand did not change significantly from baseline.

Considering the nature of our intervention, an important outcome of this paper is the fact that by the end of the study none of our patients had been restarted on AED. Re-introduction of AED in this group of patients is not uncommonly reported and has been linked with a lack of acceptability of the diagnosis by patients, carers and GP's (Lempert et al, 1990; Walczak et al, 1995; Jongsma, 1999; O'Malley, 2000). Accepting the diagnosis of PNES is in itself important for engagement with future treatment (Sirven & Glosser, 1998; O'Malley et al, 2000) and also has been associated with good prognosis (Ettinger et al, 1999). Our management appears therefore to have been successful in removing the label of "epilepsy" and helped patients to accept the diagnosis of PNES.

6.5.1. Psychosocial outcomes

At the end of the study the anxiety scores of the HADS had remained stable however the depression scores had significantly improved. Although a statistically significant change the clinical impact of the reduction of depression scores is modest if compared with the effect size expected in trials of antidepressants.

Interestingly the post hoc analysis showed that attack free patients were more likely to have lower scores of depression; it can be argued that the reported improvement of mood is a reflection of clinical improvement. This raises the question discussed by other authors of whether the attack disorder in itself is the cause or at least a significant factor contributing to the frequently reported depressed mood of patients with PNES (Bodde et al, 2008; Fiszman & Kanner, 2010).

We also need to consider the fact that the improvement in mood could also been a result of the attention given to the subjects as part of the study. As previously discussed by LaFrance, this effect may be a particular issue in this group of patients that frequently feel rejected or accused of pretending by health professionals (Green et al, 2004; LaFrance, 2007; Thompson et al, 2009).

As part of our intervention, medication was withdrawn in all patients; continuation of AED however has been justified by some authors on the basis of the potential mood stabilising and impulse control effects of AED's (Ettinger et al, 1999; LaFrance, 2008). Our results, however, show no deterioration in mood or behaviour following the withdrawal of AED. O'Sullivan et al. also found no differences when comparing outcomes between patients on AED with mood stabilising effects or not. Our view is that the benefits of withdrawing AED in patients with PNES outweigh any hypothetical benefits from continuing a medication originally prescribed for suspected epilepsy.

In summary, we detected a significant improvement of the depression scores which may be a result of our intervention or other factors. The fact that withdrawal of medication did not result on a deterioration of mood is possibly more relevant in the context of our intervention and would support our management strategy.

In terms of illness representation, we know that patients with PNES are likely to have a more external locus of control and are less likely to see stress as a relevant factor (Goldstein et al., 2000; Stone et al., 2004). Our study showed that by 18 months subjects, had a greater internal locus of control were more likely to attribute their condition to psychological causes and were less likely to see their condition as chronic.

The changes in locus of control and attribution however did not seem to translate into clinical improvement, since by the end of the study attack free patients did not have a higher internal locus of control when compared with non-attack free patients. This finding was surprising since higher internal locus of control and reattribution to stress is an important objective of psychosocial interventions for PNES and used as markers of improvement (Goldstein et al, 2004; LaFrance et al, 2009). Since all the patients from our study, were constantly advised that PNES were caused by stress, there is a possibility that the observed shift toward a psychological explanation partly reflects a response bias rather than a true change of insight.

It is also interesting that the external locus of control did not change significantly; in fact the scores were low at baseline and remained low. It does not appear that the attribution changed for external causes to psychologically-based ones. This scale's validity was originally established in patients with chronic fatigue syndrome leading to items attributing illness to germs and pollution. As such it is possible that this particular scale (IPQ) did not cover external factors of specific relevance to our group who would might be expected to attribute their condition to, for example, a neurological disorder (Weinman, 1996).

For a future longer term outcome study an important issue would be to determine weather reattribution to stress or mental state correlated with a real shift in locus of control and insight in patients with PNES.

Finally, by the end of the study patients were less likely to see their condition as chronic, particularly for attack-free patients, which is intuitively appealing. Interestingly, a pilot study of CBT treatment with a similar number of attack-free patients showed no changes on the perception of chronicity (Goldstain et al., 2004).

A wider number of physical symptoms has been associated with poor prognosis of PNES (Reuber et al., 2004) and our results seem to corroborate this finding since by the end of our study, patients in the attack free group were reporting less symptoms when compared with patients that were still having attacks.

As part of our comprehensive psychological outcome measures, we were interested in the potential impact of AED. The negative impact of antiepileptic medication on the quality of life of patients with epilepsy is well documented (Jacoby et al., 1992; Perucca & Meador, 2005) and from that point of view patients with PNES treated with AED are exposed to the same potential side effects if not more.

We used the SEALS questionnaire which is sensitive to medication changes; however, we found no significant differences. It is possible that the SEALS questionnaire which was designed for epilepsy patients was unable to detect any differences in a distinctly different group of patients with high levels of psychopathology, including disorders of personality and other somatic symptoms as chronic pain and fatigue (Devinsky, 1996b; Galimberi, 2003; Benbadis, 2005)

6.5.2. Social outcomes

As reported by other authors the overall social outcomes of the study were poor (Reuber, 2003; O'Sullivan, 2007; Duncan & Oto, 2008; Kuyk, 2008). Some of the results, however, were encouraging, particularly the reduction of patients receiving state benefits because of PNES.

A high proportion of patients with PNES receive benefits and this has been consistently reported as factor of poor prognosis. (Kristensen, 1992; Lempert, 1999; Reuber et al., 2003b; McKenzie et al., 2009). Most outcome papers report the percentage of patients on social security benefits without any further details; however the reason for receiving benefits may have nothing to do with PNES. In this paper we distinguished between patients on social security because of the attacks only, or due to other reasons.

One of the most interesting findings from the present study is the fact that Social security benefits were stopped for most of the patients reporting PNES as the only disability. Since all these patients were initially diagnosed with epilepsy and treated accordingly with AED, a firm diagnosis of PNES followed by the

withdrawal of AED appears to have removed the epilepsy label and the need for benefits.

A significant number of patients also reported a return to the level of activity of before PNES, and these subjects were significantly more likely to be attack free. This improvement, however, has to be viewed with caution since the reported level of activity of many of our subjects had been very limited even before they developed PNES.

6.5.3. Methodological considerations

The current study has some methodological limitations and our findings need to be viewed with caution. The sample size was small, particularly considering the amount of statistical tests performed; we acknowledged this limitation and also presented the results correcting for multiple testing. However, given the exploratory and observational nature of the study, the aim was to detect potentially important differences in the first place by protecting against Type 2 error. The results of the current research therefore require confirmation by an appropriately powered study.

In terms of the characteristics of the sample, a potential confounder was the variation in chronicity amongst patients; there is evidence that the length of the disorder has an impact on outcome (Lempert, 1990; Buchanan, 1993; Walczak, 1995) although this has also been disputed (McKenzie, 2010). It can also be argued that eighteen months may be too short a period to detect certain changes, particularly employment and benefit status (LaFrance et al., 2006).

As part of our treatment protocol, all our subjects were offered up to 6 sessions with clinical psychologists, not all patients attended and only less than half completed the course. Although this was our TAU, when presenting the results of the whole group, the fact that not all patients had the same input in terms of psychotherapeutic intervention, was a potential confounder.

We also acknowledge the fact that this paper is based on an original Randomised Controlled Trial investigating the effects of withdrawing AED in patients with PNES.

The main strengths of the present study on the other hand include; the accuracy of the diagnosis and the homogeneity of the sample in terms of management and length of follow up, which is a recognised problem for most outcome and prognosis studies on PNES (Bowman, 1998; LaFrance, 2007; Bodde et al, 2008). Our sample represents a purer group of patients when compared with other larger studies (Reuber et al, 2003) since all patients had the diagnosis of PNES confirmed by video EEG and none had coexisting epilepsy.

6.6. Conclusion

With this paper we present psychosocial outcome data for a group of patients with PNES following a study design that overcomes some of the methodological problems encountered in other published studies, in terms of diagnostic rigour and sample homogeneity.

Despite the methodological limitations, the results of this observational study are encouraging; including an improvement of depression scores, a shift towards a more internal locus of control, less restricted levels of activity and a significant reduction of the number of patients receiving Social Security benefits because of PNES only.

Our main management strategy was based on the idea of diagnostic clarity and from this point of view we were successful in removing the label of epilepsy and shifting the focus to a more psychologically based explanation without destabilising the patients.

Further research, with purposely designed studies, larger samples and longer follow up periods is still needed in this area.

Chapter 7:

Discussion

7.1. Thesis findings: Summary

The subject of AED in the context of PNES is increasingly recognised as an important issue and although discussed in many review and opinion papers, there is very little original research to confirm clinical opinion. The current thesis intends to investigate the effects of the continuation or withdrawal of AED in patients with PNES. The main findings are presented in table 7.1.

Table 7.1: Key findings from current thesis.

Chapter	*Key Findings*
2	A systematic review of the literature found three observational studies reporting the continuation of AED as a prognostic factor. Two papers reported association between continuation of AED and a poor prognosis and a third paper reported no effect. Due to important methodological problems in all three studies, we were unable to reach a conclusion.
4	An observational outcome study on the safety of AED withdrawal in patients PNES, showed: - 3/78 patients presented with new attacks (complex partial seizures) during withdrawal, but were fully controlled by the end of the study - 4/78 were medically treated for prolonged attacks (significantly lower number) - 14/78 reported new symptoms after AED withdrawal. - No serious medical complications were reported - At the end of the study there was a significant reduction of attack frequency
5	An exploratory Randomised Controlled Trial evaluating the possible therapeutic effects of AED withdrawal: - 25 subjects were recruited ,14 randomised to IW and 11 to DW - The IW group had a significant reduction of the use of emergency treatment for PNES, and a lower proportion was using emergency services when compared with the DW group. The IW group was less likely to report tiredness as assessed by the IPQ. - The IW had a sustained reduction of attacks throughout the study; by the end of the study 50% were attack free as compared with 27% in the DW group (NS). - There was no evidence of clinical deterioration in the IW group or the DW group after
6	An observational study assessing the longer terms outcomes of patients with PNES showed the following significant findings: - Improvement of the depression scores of the HADS - Increase of internal locus of control and less patients reporting their condition as chronic as assessed by the IPQ - Less restricted levels of activity as well as a reduction in the number of patients receiving benefits because of PNES

Chapter 1 comprises the introduction of the thesis, which gives an overview and background to PNES. The introduction also starts to set the scene, with particular reference to the iatrogenic harm associated with the use of AED and the inappropriate medicalisation of PNES that may perpetuate symptoms and worsen prognosis.

In chapter 2, a systematic review of the literature concludes that there is a lack of good quality research and, therefore, of any reliable evidence on the effects of AED treatment in patients with PNES, justifying the need for further original research in this area.

Chapter 4 presents the results of a large observational study to establish the feasibility and safety of supervised AED withdrawal in patients with an established diagnosis of PNES. The conclusion of this study is that the withdrawal of AED is a safe intervention in terms of mortality and morbidity.

To evaluate the potential therapeutic effect of AED withdrawal we next designed a randomised controlled trial which is presented in chapter 5. The results of this exploratory trial suggested a possible therapeutic effect of AED withdrawal, with a sustained reduction of attacks following the withdrawal of medication and a significant reduction in health-care utilisation.

The last original paper, presented in chapter 6, investigates the longer term psychosocial outcome data on the whole group. The study reports significant improvement in some psychosocial measures and at the same time highlights some of the difficulties in assessing outcomes with current available measures in this heterogeneous group of patients.

This last study also presents the results of a sample of patients subject to a rigorous diagnostic procedure, a standardized management, and with equal length of follow up time. These are unusual methodological features, and indeed strengths, over most of the currently published observational studies (Kanner et al, 1999; Carton et al, 2003; Reuber at al, 2003b; O'Sullivan et al, 2006).

In conclusion, the research presented in this thesis has provided evidence that taking patients with PNES off AED, following diagnosis, is as safe as a clinical

intervention, and has potentially beneficial effects as a therapeutic intervention in the shorter and longer term for a variety of clinical and psychosocial dimensions. The RCT (chapter 5) also represents an important contribution adding to the very few methodologically sound studies in the field of PNES.

7.2. Methodological considerations

Above all, the original research presented in this thesis represents a rigorous attempt to investigate this complex and heterogeneous group of patients. Only patients diagnosed with the gold standard test were included, patients were recruited prospectively, and great emphasis was placed on ensuring the standardisation of the intervention.

Research with this group of patients however is complicated by several factors:

- A relatively low incidence, often resulting in highly selected or opportunistic samples.
- The limited availability of the main diagnostic test (Video EEG).
- The heterogeneity of the group in terms of associated psychopathology and underlying aetiology for PNES.
- The paroxysmal nature and variable course of the disorder.
- No evidence for any particular management strategy and, therefore, no gold standard.

The research presented in this thesis attempted to address some of these difficulties; however individual chapters do, admittedly, have some methodological problems which need to be discussed.

Our subjects were recruited from the only epilepsy service in the West of Scotland, most patients being referred directly by the GPs rather than tertiary referral centres and from that point of view we feel the sample population is representative of the wider PNES population. However, for the RCT only, a relatively small proportion of the patients screened were eligible for the study. Although we detected no significant differences between the two groups, it is possible that this minority of selected patients had unknown confounders.

To limit heterogeneity, only patients with video EEG confirmation of the diagnosis were included and all patients with coexisting epilepsy were excluded. Despite our efficient protocol for video EEG monitoring, this entry criteria limited our recruitment, particularly for the RCT (chapter 5).

If our entry criteria for the diagnosis of PNES had been less restrictive, we could have recruited a further 37 patients who had the clinical diagnosis of PNES but were awaiting video EEG (chapter 5). A recent RCT on CBT treatment for patients with PNES achieved the required number of subjects by sacrificing a degree of diagnostic accuracy (Goldstein et al, 2010).

The issue of differences in co-morbid psychopathology or underlying causes for PNES, was possibly less relevant for the first study (chapter 4) since we were testing the clinical safety of an intervention, and in the second study (Chapter 5) the randomisation ensured that at least both groups were similarly heterogeneous. The last study, however, represents a heterogeneous sample from that point of view.

None of the studies in this thesis were blinded in that subjects were aware of the intervention. However the observational study reported in chapter 4 had to take place with explicit consent and the pragmatic nature of the RCT and its subsequent extension entailed the presentation to patients of real world alternatives with the foreknowledge that patient expectation would be a part of the effect both in the experimental setting and beyond. In terms of other safeguards against bias all evaluations could have been independent of the principal researcher.

In terms of the psychotherapeutic interventions offered to our subjects we acknowledge that although delivered by very experienced neuro-psychologists who followed a basic agreed structure, their input was not completely standardised. This is not ideal from a scientific point of view; however in the context of the studies presented in this thesis it is possibly less relevant since our aim was to assess the initial steps of management within a neurology clinic setting focusing on a shift in medical explanation and management.

For a study looking at the further management of PNES beyond the diagnosis a strict protocol of any intervention would be essential to evaluate its effectiveness as in the case of the studies presented by LaFrance et al and Goldstein et al which we see as complementary to our studies (LaFrance et al, 2009; Goldstein et al , 2010).

To ensure treatment fidelity we agreed on a series of scripts for all patients' contacts, it proved however impossible to perform an analysis of its delivery.

Finally, since recruitment for the RCT was so difficult, strenuous efforts to ensure retention were undertaken to ensure the viability of the study and the results may be a reflection of a Hawthorne effect deriving from this added attention and effort. Other authors have recognised this problem (LaFrance et al, 2009; Goldstein et al, 2010).

7.2.1. Outcome measures

Choosing relevant and valid outcome measure for this group of patients is complicated. As discussed by other authors, the choice of measures has to balance comprehensiveness with practicality (Quigg et al, 2002; Reuber et al, 2005; LaFrance et al, 2006).

Seizure freedom and to a lesser extent attack reduction are recognised as objective and valid measures of improvement, however, as already discussed in this thesis they are not comprehensive enough as isolated outcomes. Broader psychosocial outcomes are necessary to evaluate improvement and outcome of patients with PNES (La France et al, 2006).

On the one hand, adding a wide range of outcome measure would ensure a more comprehensive assessment of outcome and avoid missing potentially important changes due to the intervention. On the other hand, a large number of measures can compromise statistical power, a particularly relevant point in this field, where prospective recruitment of large number of patients is difficult.

A consensus statement form a group of experts following a workshop on the development of treatment for PNES suggested a list of measures which are

listed in table 7.2. The use of standardised measures, with solid psychometric properties and sensitivity to the intended treatment change, was also recommended.

Table 7.2: Potential outcome variables for treatment studies of PNES.

1	Attack frequency
2	Individual concerns
3	Employment status
4	Psychiatric symptoms and personality characteristics
5	Health related quality of life
6	Psychophysiologycal variables (e.g., arousal)
7	Family/psychosocial factors
8	Healthcare utilisation
9	Illness cognition /representation

For the three studies included in this thesis our choice of measures aimed to be comprehensive, combining attack frequency with a variety of psychosocial outcome measures, and covered most of the domains suggested in table 7.2. We chose a number of standardised scales as well as relying on self reports for some domains.

In terms of standardised questionnaires, we had to use available measures from other areas since there are no scales specifically designed to assess PNES. The IPQ had been validated for other somatisation disorders (e.g. ME); the SEALS was designed to evaluate quality of life in patients with epilepsy, taking into account the side effects of AED; and the HADS had been previously used for patients with PNES to assess mood changes.

Using scales designed for patients with epilepsy has some logic, since epilepsy is also a paroxysmal disorder which has an important impact on patient's quality of life (Jacoby et al, 2009). Patients with PNES, however, have different characteristics when compared with patients with epilepsy, with a higher proportion with personality disorders, higher levels of somatisation as well as distinct ways of perceiving and expressing their distress (Frances et al, 1999; Reuber, 2003; Galimberti et al, 2003; Binzer et al, 2004). The SEALS

questionnaire was an appropriate choice for our research, particularly since we were interested in outcomes associated with AED, although it is possible that with so much 'background noise' from the study population, this questionnaire was not sensitive enough to detect changes.

The IPQ on the other hand was designed to assess illness beliefs for a wide variety of illnesses and is validated for a somatoform disorder (ME). There is no doubt that assessing illness beliefs in PNES patients is important, particularly since our hypothesis was based on how continuation of AED affects patients' understanding of their disorder, however there are some considerations that need to be made.

The version of the IPQ which we used had some problems that have since been addressed in a revised version, but this was unavailable at the time. (MossMorris et al, 2002). As well as strengthening the psychometric properties of the scale, a cyclical time line subscale was included for paroxysmal disorders which would obviously have been of particular relevance to PNES.

However, for all versions of the IPQ, researchers are encouraged to adapt the scale to their particular subject. In retrospect it would have been interesting to add symptoms in the 'identity subscale' relevant to the attack disorder, and a question in the 'cause subscale' referring to epilepsy as a possible cause.

For the social outcomes measures we relied on patient self reports, corroborated by relatives, as well as including more objective measures like employment status and ability to attend the clinic alone. Other authors have used validated scales to assess social adjustment and disability like the Work and Social Adjustment Scale (Mundt, 2002) or the SF- 36 (Ware & Sherbourne, 1992) which are validated instruments, are relatively short and easy to use (Goldstein et al, 2004). Using one of these scales could have added more rigour to our studies.

We felt that health care utilisation was another important outcome to measure and, for the sake of clarity, we concentrated mainly on emergency contacts. The use of a scale however would have allowed an estimation of the costs and more

important the savings resulting of our intervention, relative to say other interventions for standardised comparisons.

A difficulty in choosing specific standardised measures to assess outcomes in the studies presented in this thesis is the fact that some of the potentially relevant factors may be difficult to measure using an existing scale. In this context, the use of qualitative methods would have allowed a more comprehensive exploration of the impact that giving the diagnosis of PNES and withdrawing medication has in this group of patients.

Our assessments were all quantitative and as such we perhaps lacked the ability to conduct a more fine grained enquiry into patients' views. It would have been useful to elicit patients views of their condition and the impact of our intervention (AED withdrawal) and relate this to their outcome in the study.

In early discussions around the design of the study it was proposed that at recruitment qualitative methodology be employed to explore patient perceptions of the role of AED prescription and withdrawal. Unfortunately resources were not available to conduct interviews and subsequent analysis along the lines of classical qualitative research. A more modest qualitative approach could perhaps have been adopted by eliciting the views of patients as the study progressed and then using these views as a basis for items in the baseline or follow up assessments of subsequent patients. However it was felt that this approach, which would effectively have meant that the nature of the assessment evolved as the study progressed, would have compromised the reliability and validity of our assessments.

In summary, the quality of studies presented in this thesis could have been enhanced by the use of; the IPQ-R version, a validated scale to measure social adjustment, and a more comprehensive measure of health-care utilisation. The use of qualitative measures would have also allowed a more fine grained and evocative account of the patient experience.

7.3. Clinical implications

The findings of the body of work presented in this thesis are relevant to clinical practice, since this research was conducted in a real life clinical setting comparable to most regional epilepsy services, where most patients with PNES are assessed and treated.

Overall, it is hoped that this research raises awareness of the very serious issue of iatrogenic harm. Our three studies have shown that a clear diagnosis and consistent management of PNES results in a reduction of health-care utilisation, specifically a reduction of emergency services and treatment of pseudo status. It is important to stress that our intervention was relatively simple and achievable and that these positive results were maintained at follow up.

The study presented in chapter 4 demonstrates that AED withdrawal in patients with PNES is a safe clinical intervention. This paper, published by the JJNP and was the editor's choice at the time, has already proved to have influenced scientific opinion, and continues to be referenced in many papers as the main evidence to guide physicians who wish to withdraw AED in a safe manner. It will take some time however to determine if indeed clinicians are more likely to take patients off AED.

The results of the exploratory randomised control trial (chapter 5) also show the importance of withdrawing medication to limit iatrogenic harm, in this case, when compared with delayed withdrawal, a pragmatic alternative. The impact of the intervention can be illustrated by the experience of one of the participants; patient X was randomised to delayed withdrawal, she had three admissions to ITU in the past and had been repeatedly treated for prolonged PNES in hospital. For the first 9 months after the diagnosis she continued to use emergency medication for prolonged attacks and was treated on two occasions in Accident and Emergency despite showing a letter with a clear explanation of her diagnosis of not epilepsy. From 9 months onwards however as she came off her medication there was no contact for emergency services or use of Benzodiazepines to treat prolonged events although she continued to have attacks.

The above anecdotal illustration encapsulates the idea behind much of this thesis research. Underpinning our research is the idea that, the use of medication as a treatment for a disorder has powerful effects, not just at a physiological level but affecting patient's behaviour and their understanding of their disorder.

Finally, with the last paper (chapter 6), we can reassure clinicians that withdrawal of AED after the diagnosis is not only safe as a clinical intervention, but also does not result in a negative psychological impact. This last study also gives an interesting insight into the potential pitfalls of illness reattribution. As one of the objectives of therapy, the reattribution of PNES to stress has only value if it reflects a real change in locus of control and commitment to recovery.

In summary the work presented in this thesis has helped to establish AED withdrawal as an intervention in its own right. AED withdrawal should therefore be included in current and future protocols of the initial management and taken into consideration in future treatment studies.

7.3.1. PNES in the context of other medically unexplained symptoms (MUS)

Medically unexplained symptoms (MUS) are common in neurology clinics and the overall outcome is also poor (Carson et al, 2003; Sharp et al, 2010).

As pointed out by other authors, knowledge from current studies on other MUS could be a good source of information for the development of effective treatments for PNES. Conversely, knowledge of PNES can also contribute to our understanding of other somatisation disorders.

PNES have the distinct characteristic of having a sensitive and specific diagnostic test which other disorders, like pain or fatigue, do not have. The diagnostic certainty of PNES makes research on iatrogenic harm or on the effects of over treatment much easier; the results however can also be applied to other MUS.

Lessons could be learned then from the research presented in this thesis, since iatrogenic harm is a universal problem in medically unexplained symptoms with

a majority of patients treated with multiple drugs or surgery, and, as in PNES, the evidence for an effective treatment is sparse (Barsky & Borus, 1999; Mayou et al, 2000).

The research presented in this thesis shows that, a clear explanation and a removal of a treatment intended for an erroneously diagnosed physical illness, greatly reduces iatrogenic harm and has a positive effect on psychological outcomes as well as reducing symptoms.

If nothing else this thesis should inform physicians of what not to do. Treating patients for something they do not have potentially does more physical and psychological harm than no treatment at all.

7.4. Future directions

There is no doubt that further research on the management of PNES is required, however, it is unlikely that any single intervention beyond the presentation of the diagnosis and removal of AED would be suitable for all patients.

As a result of a workshop to discuss the development of treatment for patients with PNES, a three arm trial comparing regular review by neurology with CBT or antidepressants was proposed (LaFrance et al, 2006). To achieve the power necessary to detect changes in such a varied population, this would have to be a multi-centre trial.

For a multi centre trial, however, the diagnostic accuracy of PNES would be an issue; to ensure the quality of the diagnosis the gold standard technique of video EEG would be required. As shown in this thesis, the use of video EEG is a factor that limits recruitment.

Targeting or excluding specific subgroups of patients (for example people with a personality disorder, multiple other MUS, chronic symptoms) would make future studies easier to achieve in terms of retention and sample variance, however this would limit their relevance.

A multi-centre pragmatic trial with a study design reflecting the stepped care model approach seems the only way forward to conduct further research on management of PNES with sufficient power.

Following video EEG confirmation of the diagnosis of PNES, all patients would be initially randomised to a comprehensive protocol for the delivery of the diagnosis of PNES (clear and supportive explanation, basic psycho education and written information) or to a clear however basic explanation accompanied by written information, offered by the treating neurologist within the constrains of a general neurology clinic. For patients on AED the withdrawal of the medication would be immediate or delayed..

Following this first phase patients whose attacks continued would be re-randomised to a course of CBT or treatment with an SSRI. The group of attack free patients would remain as a control group and reviewed at the end of phase two.

Power to detect a moderate effect would be substantially diluted by the third of patients who seem to respond regardless of the intervention.

Follow up of all patients should be at least two years long because of the often reported longer term deterioration of some early responders.

Clinical outcomes should be attack freedom, health care utilisation drug and AED use and evidence of new physical symptom. Psychosocial outcome should include measures of; social functioning, anxiety and depression as well as measures reflection insight into the diagnosis of PNES and shifts of locus of control. Ideally an initial psychiatric screening would be also useful.

The above study as well as researching the effectiveness of the different management interventions would also allow an initial exploration of possible predictors of outcome and identification of subgroups of patient which are more likely to respond to particular management strategies

The above represents a gold standard and may not be practically achievable. However, there are still many unanswered questions that could be addressed

through more modest studies, further research on; patients illness beliefs as well as doctors beliefs; cultural bound differences; the influence of underlying psychopathology or the natural course of PNES amongst others. All of these have been only minimally explored and could increase our understanding of PNES and help towards the design of a larger study on the management of PNES.

Alternatively there may be some value in a complete paradigm shift and consider PNES as one of the phenotypical expressions of somatisation as some authors have argued (Wessely, 2004). If we conceptualise PNES as one more of the functional somatic symptoms, generic research including all medically unexplained symptoms could be the way forward.

Appendices

Appendix A: Checklist for the assessment of quality of observational studies on the outcome of psychogenic nonepileptic seizures.

1-Is the study based on a representative sample selected from a relevant population of patients with NES

Yes

No

2-Are the criteria for inclusion explicit

Yes

No

3-Were patients with co-existing epilepsy excluded

Yes

No

4-Was there an established reliable system for selecting all the cases

Yes

No

5-Was the diagnosis of NES confirmed by video-EEG Case definition

Yes

No

6-Did all individual entered the survey at a similar point on time in the diseases progression

Yes

No

7-Was the sample size >75

Yes

No

8-Was the follow up sufficiently long to assess improvement of NES

Yes

No

9-Were cases assessed at a similar point after the diagnosis?

Yes

No

10-Was the proportion of the sample followed up >60%

Yes

No

11-Were all subjects exposed to the same intervention or standardised management

Yes

No

12-Were the outcome measures valid and comprehensive (including other than attack reduction)

Yes

No

13 Were tall the outcome measures clearly stated?

Yes

No

14-Did the authors used objective measures of outcome (attack diary, rating scales) ?

Yes

No

Appendix B: Checklist for reports of observational studies (STROBE statement)

Title and abstract	a/Indicate the study design b/Provide an informative and balanced summary
Introduction	
Background	Explain scientific background and rationale
Objectives	State specific objective and prespecified hypothesis
Methods	Present key elements of the study
Study design	
Settings	Describe setting, location and relevant dates
Participants	Give eligibility criteria and the source and method of data collection
Variables	Define all outcomes, exposure, predictors and potential confounders as well as diagnostic criteria
Data source/measurements	For each variable give sources of data and details of methods of assessment
Bias	
Study size	Describe any efforts to address potential bias
Quantitative variables	Explain how the study size was arrived at Explain how quantitative variables were handled in the analysis
Statistical methods	a/Describe all statistical methods, including those used to control confounding b/Explain how missing data was addressed c/Describe methods used to examine subgroups and interactions
Results	
Participants	a/Report number of individuals at each stage of study b/give reasons for none participants c/Consider use of a flow diagram
Descriptive data	a/Give characteristics if the study participants b/Indicate number of participants with massing data for each variable
Outcome data	Report numbers of outcomes events or summary measures
Main results	Give unadjusted estimates and confounder adjusted estimates
Other analysis	Report other analysis done
Discussion	
Key results	Summarise key results with reference to study objectives
Limitations	Discuss limitations of the study, taking into account sources of potential bias
Interpretation	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity if analysis and results form similar studies
Generalisability	Discuss the generalisability(external validity)of the study

Appendix C: Patient information sheet on PNES.

NON EPILEPTIC SEIZURES – patient information

As we discussed at the clinic you know now that the results of the test show that your attacks are not epileptic. You have Non Epileptic Seizures (NES) or Pseudoseizures.

Many of the people that we see in this clinic have been told that they suffer from an illness called epilepsy. Other people have never been given a clear answer at all.

With this leaflet we are hoping to answer some of the questions that you may have about this condition.

1-What are Non Epileptic Seizures?

These are turns that look like epileptic attacks and in fact are often mistaken for epilepsy but, unlike epilepsy, the cause is not due to something being wrong with your brain waves. These attacks are caused by psychological problems (stress, emotional problems, worries).

This is not an uncommon problem. We run a clinic especially for people with these kind of attacks and we can see up to three new patients a week.

In fact about two out of ten people who are thought to have untreatable epilepsy suffer from non epileptic seizures.

2-What do you mean by a psychological or emotional cause?

You may find it very difficult to understand how these attacks are caused by stress or to think of any causes for your turns.

The relationship between your emotional upset or stress and the attack is not always straightforward

Our body can show stress or distress in a very physical way. For example some people can be physically sick because of worry. The person is being sick but the cause is not due to a stomach problem but to stress.

Stress and worries can build up, sometime without a person being aware of it. But it may build up to a point that the pressure is too much and you have an attack to let go off the pressure .
We can think of these turns as a way of coping, like a pressure release valve or “time out”.

3-Does that means that I am putting them on?

NO

These attacks are a very real problem but the root of the problem is emotional, not physical.

The fact that there is not a physical cause for your attacks does not mean that you are “mad” or pretending. What it may mean is that your are more upset or stressed than you realise.

Having these attacks can be very unpleasant and upsetting as well as making you day-to-day life very difficult.

4-What makes me have these attacks?

For some people the problem is related to an unpleasant or traumatic experience from the past. For others it can be due to a number of different problems.

In some people it takes some time before we find the underlying problems.

5-What about the result of the test ?

Recording an attack during a Video EEG test is the best test we have for the diagnosis of NES. Is very accurate and we can trust the results

With this test we are able to monitor your brain waves and take a video at the same time

Your brain waves change depending if you are awake, asleep or even drowsy. By looking at you brain waves during an attack we can tell if you are unconscious or there is something affecting the way your brain works.

The test has shown that your brain waves did not change or become epileptic before during or after the attacks we recorded. This confirms the diagnosis of Non Epileptic Seizures.

6-How come I was told that I had epilepsy?
(by doctors, nurses and paramedics)

The diagnosis of your type of attacks can be difficult. Because the attacks can look so much like epilepsy, they are often confused and treated as epilepsy.

However we now know that NES is not a rare condition. A psychological cause has to be considered when patients present with attacks that seem difficult to control with medication.
Better tests are also available nowadays to help us with the diagnosis.

7-Can Non Epileptic Seizures be treated?

This kind of attack can often be successfully treated. There are a number of things we can do to make sure you have a good result.

Some people improve just by having a clear answer and explanation for the attacks. Knowing what’s wrong with you is helpful in itself .

We think that being looked after by the same people is important for a successful recovery. We will support you through the recovery process and will not pass you on to any other doctors.

You will also be able to see one of the two psychologists on our team. They are experienced at helping people with your kind of attacks.
The psychologist will help you to find the cause (s) for your attacks and will also help you to have control over the attacks.

9-What can this clinic do for me?

- Give you a clear answer about the cause of you attacks
- Help you to gain control over the attacks
- Give you support
- Give you advice on practical matters such as driving and work

IF YOU HAVE ANY FURTHER QUESTIONS PLEASE CONTACT DR MARIA OTO AT:

PHONE:

Appendix D: Drug withdrawal protocol.

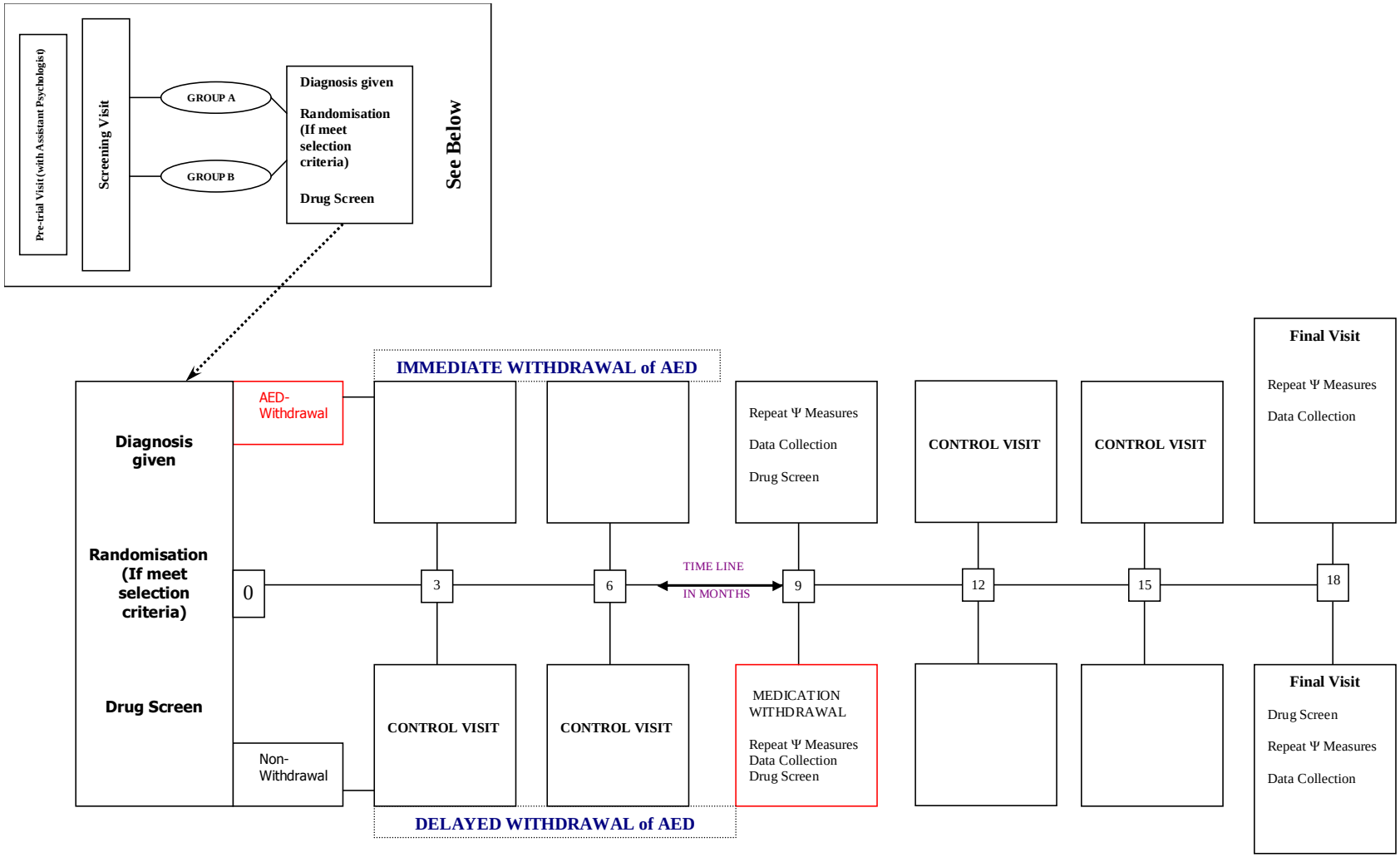
Drug withdrawal protocol

Withdrawal programme agreed and discussed with patient
Patients and primary care physicians given written withdrawal programme
Patients, relatives and primary care physicians instructed to report any new event type to the clinic
Contact phone number supplied
Clinical follow up at 3 monthly intervals
Psychology treatment programme of 2-6 visits during study period

Drug withdrawal schedules

Phenytoin
100mg/week till dose is 100mg/day, then 25mg per week
Carbamazepine
200mg/week till dose is 1000mg/day, then 100mg/week
Sodium valproate
500mg/week till dose is 500mg, then 200mg/week
Vigabatrin
500mg every 2 weeks until dose is 500mg, then 500mg alternated days for 2 weeks
Lamotrigine
100mg/week till dose is 300mg, 50mg/week till dose is 50mg, then 25mg/week
Gabapentin
800mg/week till dose is 1200mg, then 400mg/week
Topiramate
100mg/week till dose is 200mg, 50mg/week till dose is 50mg, then 25mg/week
Levetiracetam
500mg/week till dose is 1000mg, then 250mg/week

Appendix E: RCT study design



Appendix F: CONSORT Checklist of items to include when reporting a randomized trial

PAPER SECTION And topic	Item	Description	Reported on Page #
TITLE & ABSTRACT	1	How participants were allocated to interventions (*e.g.*, "random allocation", "randomized", or "randomly assigned").	
INTRODUCTION Background	2	Scientific background and explanation of rationale.	
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	
Objectives	5	Specific objectives and hypotheses.	
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors).	
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	
Randomization -- Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (*e.g.*, blocking, stratification)	
Randomization -- Allocation concealment	9	Method used to implement the random allocation sequence (*e.g.*, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	
Randomization -- Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.	
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.	
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	
Recruitment	14	Dates defining the periods of recruitment and follow-up.	
Baseline data	15	Baseline demographic and clinical characteristics of each group.	
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in	

Appendix G: Diagnostic criteria and diagnostic process for PNES.

The diagnostic process considered not only the diagnosis of nonepileptic seizures (NES) but also the diagnosis of possible coexisting epilepsy.

An initial “provisional” clinical diagnosis of NES was made following an assessment by an epilepsy specialist, based on witness descriptions of all attacks and the patient account. The definite diagnose of NES was established following the recording of a typical attack during video EEG monitoring.

The epilepsy specialist also assessed the patient for any evidence of current or past epilepsy (one of the exclusion criteria for the study) by reviewing clinical records and the reports of previous EEG and the descriptions of past attacks.

To ensure the accuracy of the diagnosis the following criteria which were agreed by the team of senior epileptiologists was applied.

Diagnostic criteria for Epilepsy.

•Reports of attacks before the age of 12 years.
•Description of past or present attacks (by patient, eyewitness or reported in the notes) compatible with epileptic seizures.
•Interictal epileptiform abnormalities in past or current EEG (as agreed by a neurophysiologist and an epilepsy specialist)
•Video EEG recording of any attack with associated EEG epileptic discharges.

Any EEG reported as abnormal in the past this will be reviewed and reported by a nerophysiologyst.

Diagnostic criteria for NES

•Attack descriptions compatible with known clinical presentation of pseudoseizures (e.g. alternating movements, pelvic thrusting, and emotional content).

•Video recording of attack semiology was available and compatible with eyewitness account.

•EEG record of attack showed no modification or associated EEG abnormalities.

•ECG recording showed no arrhythmia during the attack (tachycardia acceptable if all other features compatible with pseudoseizure).

Diagnostic accuracy and diagnostic process

To minimize the risk of diagnosis error at least three clinicians (two epilepsy specialists and a neurophysiologist) were involved in the diagnostic process and each clinician assessed each case independently.

The definitive diagnosis depended on video EEG confirmation of the provisional clinical diagnosis. Until we had been able to record all types of typical events on video EEG, the diagnosis of NES was not given to the patients.

Before presenting the diagnosis to the patients, all cases were routinely discussed at the “epilepsy team clinical meeting” (attended by all epilepsy specialist and neurophysiologists). Video recordings and EEG’s were reviewed at that point.

In some cases if there are doubts about diagnosis or there are conflicting opinions from the physicians involved, patients were discussed separately at the NES clinical meeting. Were a more formal presentation of the case including the results of all past and present investigations were reviewed and a decision was reached by consensus of all the physicians involved...

Appendix H: RCT protocol.

An exploratory randomised controlled trial of withdrawal of antiepileptic drugs (AED) in patients with PNES.

PROTOCOL

Referral process

All new referrals will be sent an appointment to attend the PNES clinic. Subjects will see the research assistant for administration of psychological measures followed by their 1st appointment with the research fellow.

The appointment letter will contain a diary for the patient to prospectively record attack frequency prior to the PNES clinic appointment.

Patient will be seen within 8 weeks of referral.

The research assistant will call all those referred (with available telephone numbers) at the time of appointment allocation to collect 2-month retrospective information (historic attack frequency and healthcare utilisation)

Screening: Pre-trial visit

Psychology assistant:

Administer psychological rating scales
-NART
-SEALS
-HADS
-ILLNESS PERCEPTION QUESTIONNAIRE

Collect information regarding healthcare utilisation over the previous 6 months:
-Out of hours and emergency health contacts for PNES or other and use of rescue drugs for NES

First Visit (immediately after pre-trial visit)

Patient seen by the Research Fellow who will review medical records and gather routine clinical information, in order to establish a provisional clinical diagnosis. The provisional clinical diagnosis will be one of the following: Epilepsy or PNES or Epilepsy and PNES

Group A: Patients that at the time of referral had the diagnosis of PNES confirmed by Video EEG

-Patient counselled and information about the trial given.
-Patient consent ascertained.
-Randomised to immediate or delayed withdrawal of AED: randomization will be by the EEG secretary using a random number list.
-Phased withdrawal begins in immediate withdrawal group (see attached drug withdrawal protocol).
-Phased withdrawal in delayed group will commence 9 months later
-Anti-epileptic drug levels checked in both groups to monitor compliance.
-To send a standard letter informing GP about the trial (see attached letter).

Group B: Patients that following the screening visit have a provisional clinical diagnosis of PNES without video EEG confirmation

All these patients will be referred for video EEG monitoring. Once the diagnosis is confirmed the same procedure as outlined for Group A takes place.

TRIAL VISITS SCHEDULE

Immediate withdrawal arm:

0 months (trial visit 1) - RANDOMISATION VISIT. Commence withdrawal of AED.

3 months (trial visit 2) - Monitor withdrawal and collect data on seizure frequency and health care utilisation.

6 months (trial visit 3) - Monitor withdrawal and collect data on seizure frequency and health care utilisation.

9 months (trial visit 4) - Collect data on seizure frequency and health care utilisation. Psychological rating scales re-administered and check blood drug levels.

12 months (trial visit 5) - Control visit. Collect data on seizure frequency and health care utilisation.

15 months (trial visit 6) - Control visit. Collect data on seizure frequency and health care utilisation

18 months (trial visit 7) - FINAL VISIT. Collect data on seizure frequency, health care utilisation and social functioning. Psychological rating scales re-administered.

Delayed withdrawal arm:

0 months (trial visit 1)- RANDOMIZATION VISIT.

3 months (trial visit 2) - Control visit. Collect data on seizure frequency and health care utilisation.

6 months (trial visit 3) - Control visit. Collect data on seizure frequency and health care utilisation.

9 months (trial visit 4) - Commence withdrawal of AED. Collect data on seizure frequency and health care utilisation. Psychological Rating Scales re-administered and check drug blood levels.

12 month (trial visit 5) - Monitor withdrawal and collect data on seizure frequency and health care utilisation.

15 months (trial visit 6)- Monitor withdrawal and collect data on seizure frequency and health care utilisation.

18 months (trial visit 7) - FINAL VISIT. Collect data on seizure frequency, health care utilisation and social functioning. Psychological rating scales re-administered and check drug blood levels.

Appendix I: Patient consent form for RCT.

CONSENT FORM

I have read the information sheet attached for the anti-epileptic drug withdrawal study.

I know that I do not have to take part in this study. I am aware that if I choose not to take part my treatment will not be affected in any way.

By signing this form I am agreeing to take part in the study. However, I can withdraw from the study at any time by letting my doctor know.

Signed_____ Date_____

Witness signature

Signed_____ Date_____

CONSENT FORM

I have read the information sheet attached for the anti-epileptic drug withdrawal study.

I know that I do not have to take part in this study. I am aware that if I choose not to take part my treatment will not be affected in any way.

By signing this form I am agreeing to take part in the study. However, I can withdraw from the study at any time by letting my doctor know.

Signed_____ Date_____

Witness signature

Signed_____ Date_____

Appendix J: Scripts for study visits.

Presenting the diagnosis of NES: The same for all subjects

Step 1
Review the results of video EEG to confirm that the attacks recorded are typical and that all have been recorded.

Step 2
The good news:“this attacks are not epilepsy “
Explanation of the EEG results and emphasise the accuracy of our diagnosis

Step 3
Explain the nature of attacks: Attacks that resemble and are often confused by epilepsy however the cause is not an abnormal discharge of electricity in the brain but a result of psychological difficulties

Normalise and instil hope –It is a common condition and we see and help many patients with this disorder
Explanation of underlying mechanism using the model of predisposing, precipitating and perpetuating factors.

Step 4
Answer questions referring to our information leaflet created following

Step 5
Discuss management and research project and give written information. The patients information for the DW group will not have the question answer of medication.

SCRIPT FOR VISITS: 3 and 6 months

AED delayed withdrawal group:

1-“How are you feeling at the moment?,(asked to rate using an interval scale from 1-10)

2- Have you had any turns since last appointment? Can I see you diary?"

-If there has been a reduction of attacks: "this is very encouraging there is already improvement in only twelve weeks, you are doing very well"

-If there has been no improvement, (try not to put too much emphasis on number of attacks):"At this stage we often don't see a difference on the numbers of attacks, is OK, these can take time"

3-"Have you been taken to hospital, called an ambulance or been given emergency medication because of the turns since the last appointment?"

-If the answer is no, positive reinforcement particularly to the carer" That is really good, this shows that things are getting better. Its very important that you keep away from emergency ambulances and casualty departments "

-If the answer is yes, go over again with patient and carer (assertive way)" It's very important that you keep away from ambulances and casualty departments. As we discussed you will not come to any harm through the attacks and the best way to deal with it is to leave the person alone, you will come round in your own time any contact with emergency services will complicate matters and potentially make you worse it's important that everyone understands that this is not epilepsy"

4-How do you feel now about the diagnosis? Depending on the degree of resistance to the diagnosis at this point go over a number or all the points made at the initial consultation about diagnosis and cause of PNES.

5-Have you any new problems since I last saw you? Are you on any new drugs? (if new physical complaint ,record but do not show too much interest) 6-Have you got any questions for me?

7-I will see you in X months time, but get in touch before if there is a problem. Make sure that you keep your diary up to date.

<u>AED immediate withdrawal group:</u>

1-Hour are you, feeling? ,(asked to rate using an interval scale from 1-10)

2-How are you getting on with the reduction of the medication, any problems? Find out current medication and give written instructions of further reduction.

3-Have you had any turns since the last appointment? Can I see your diary?"

-If there has been a reduction of attacks:" this is very encouraging there is already an improvement in only twelve weeks, you are doing very well"

-If there has been no improvement, (try not to put too much emphasis on number of attacks):"At this stage we often don't see a difference on the numbers of attacks, is OK, these can take time"

4-Have you been taken to hospital, called an ambulance or been given emergency medication because of the turns since the last appointment?"

-If the answer is no, positive reinforcement particularly to the carer" That is really good, this shows that things are getting better. Is very important that you keep away from emergency ambulances and casualty departments "

-If the answer is yes, go over again with patient and carer (assertive way)" Its very important that you keep away from emergency ambulances and casualty departments. As we discussed you will not come to any harm through the attacks and the best way to deal with it is to leave the person alone, you will come round in your own time Any contact with emergency services will complicate matters and potentially make you worse Its important that everyone understands that this is not epilepsy"

5-How do you feel about the diagnosis now? Depending on the degree of resistance to the diagnosis at this point go over a number of all the points made at the first consultation about diagnosis and cause of NES .

6-Have you any new problems since I last saw you? Are you on any new medication? (if any new physical complaint ,record but do not show too much interest)

7-Have you any other questions?

8-I will see you in X months time, but get in touch before if there is a problem. Make sure that you keep you diary up to date.

SCRIPT FOR VISIT: 9 months

Delayed withdrawal group

1-How are you feeling? ,(asked to rate using an interval scale from 1-10)

2-As we discussed this visit will be longer since we would like you to complete the questionnaires again .At this important stage of you treatment we need to assess your progress by collecting all this information again and compare it with your previous results .We will also repeat the blood tests .

3-I will also ask you to start withdrawing the tablets from now on. We will take you off one medicine at a time gradually following this protocol. I will give you

written instructions on how to reduce the tablets. Do you have any worries about coming off medication at this point (if yes answer questions and reassure)

4-Have you had any turns since last appointment? Can I see you diary?"

If there has been a reduction of attacks:"this is very encouraging there is already an improvement in only four weeks, you are doing very well"

If there has been no improvement, (try not to put too much emphasis on number of attacks):"At this stage we often don't see a difference on the numbers of attacks, is OK, this can take time"

5-Have you been taken to hospital, called an ambulance or been given emergency medication because the turns since last appointment?"

If the answer is no, positive reinforcement particularly to the carer" That is really good this shows that things are getting better. Is very important that you keep away from emergency ambulances and casualty departments "

If the answer is yes, go over again with patient and carer (assertive way)" Is very important that you keep away from emergency ambulances and casualty departments. As we discussed you will not come of any harm through the attacks and the best way to deal with it is to leave the person alone, you will come round in your own time any contact with emergency services will complicate matters and potentially make you worse Is important that everyone understands that this is not epilepsy"

6-How do you feel now about the diagnosis? Depending on the degree of resistance to the diagnosis at this point go over a number or all the points made at the first consultation about diagnosis and cause of PNES .

7-Have you had any new problems/symptoms since I last saw you? Are on any new medication?

8-Have you got any other questions?

9-I will see you in X month's time, but get in touch before if a new problem arises. Make sure that you keep you diary up to date.

Immediate withdrawal group

1-How are you feeling? ,(asked to rate using an interval scale from 1-10)

2-As we discussed this visit will be longer since we would like you to complete the questionnaires again .At this important stage of you treatment we need to assess your progress by collecting all this information again and compare it with your previous results .We will also repeat the blood tests .

3-You have now been of the tablets for sometime, any problems?

4-Have you had any turns since last appointment? Can I see you diary?"

If there has been a reduction of attacks:"this is very encouraging there is already an improvement in only four weeks, you are doing very well"

If there has been no improvement, (try not to put too much emphasis on number of attacks):"At this stage we often don't see a difference on the numbers of attacks, is OK, this things take time"

5-Have you been taken to hospital, called an ambulance or seen you GP because the turns since last appointment?"

If the answer is no, positive reinforcement particularly to the carer" That is really good this shows that things are getting better. Is very important that you keep away from emergency ambulances and casualty departments "

If the answer is yes, go over again with patient and carer (assertive way)" Is very important that you keep away from emergency ambulances and casualty departments. As we discussed you will not come of any harm through the attacks and the best way to deal with it is to leave the person alone, you will come round in your own time Any contact with emergency services will complicate matters and potentially make you worse Is important that everyone understands that this is not epilepsy"

6-How do you feel now about the diagnosis? Depending on the degree of resistance to the diagnosis at this point go over a number or all the points made at the first consultation about diagnosis and cause of NES.

7-Have you had any new problems since I last saw you? Are on any new medication? (if new physical complaint ,record but do not show too much interest)

8-Have you any other questions?

9-I will see you in X month's time, but get in touch before if there is a problem. Make sure that you keep you diary up to date.

VISITS AT 12 AND 15 MONTHS FROM DIAGNOSIS

Repeat the same script of visits at 3 and 6 months.

FINAL VISIT at 18 months

Same format as visit at 9 months also discuss discharge or need for further follow up.

Appendix K: Patient information sheet about RCT.

Information Sheet

The tests that you have had show that your attacks are not due to epilepsy. They also show that your brain is working normally during the attacks, which means that the attacks have an emotional cause.

This kind of attack can often be treated successfully, and there are a number of things we do to make sure that you have a good result.

We think it is sensible to withdraw your anti-epileptic medication, but we do not know whether this in itself is beneficial to your type of attacks.

We are carrying out a study to measure the effects of this, and would like you to participate.

We divide our patients into:

1. Those who come off medication straight away and
2. Those who stay on their medication for 9 months, and then come off of it.

If you agree to take part you will go into one or other group.

The group you go into will be chosen by chance.

Your treatment programme will otherwise be exactly the same.

You should be clear that you are entirely free not to take part in this study, and if you do not then your treatment will not be affected in any way. The same applies if you find you want to withdraw from the study part way through it: all you have to do is let your doctor know.

H A D Scale

Read each item and place a tick in the box opposite the reply which comes closest to how you have been feeling in the past week.
Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.
Tick only one box in each section

1. I feel tense or "wound up"
- Most of the time . . . . . ☐
- A lot of the time . . . . . ☐
- Time to Time, Occasionally . . . . . ☐
- Not at all . . . . . ☐

2. I still enjoy the things I used to enjoy
- Definitely as much. . . . . ☐
- Not quite as much. . . . . ☐
- Only a little. . . . . ☐
- Hardly at all . . . . . ☐

3. I get a sort of frightened feeling as if something awful is about to happen
- Very definitely and quite badly . . . ☐
- Yes, but not too badly . . . . . ☐
- Time to Time, Occasionally . . . . . ☐
- Not at all . . . . . ☐

4. I can laugh and see the funny side of things
- As much as I always could . . . . . ☐
- Not quite so much now . . . . . ☐
- Definitely not so much now . . . . . ☐
- Not at all . . . . . ☐

5. Worrying thoughts go through my mind
- A great deal of the time . . . . . ☐
- A lot of the time . . . . . ☐
- From time to time but not too often ☐
- Only occasionally . . . . . ☐

6. I feel cheerful
- Not at all . . . . . ☐
- Not often . . . . . ☐
- Sometimes . . . . . ☐
- Most of the time . . . . . ☐

7. I can sit at ease and feel relaxed
- Definitely . . . . . ☐
- Usually . . . . . ☐
- Not Often . . . . . ☐
- Not at all . . . . . ☐

8. I feel as if I am slowed down
- Nearly all the time . . . . . ☐
- Very often . . . . . ☐
- Sometimes . . . . . ☐
- Not at all . . . . . ☐

9. I get a sort of frightened feeling like butterflies in the stomach
- Not at all . . . . . ☐
- Occasionally . . . . . ☐
- Quite often . . . . . ☐
- Very often . . . . . ☐

10. I have lost interest in my appearance
- Definitely . . . . . ☐
- I don't take so much care as I should ☐
- I may not take quite as much care . . ☐
- I take just as much care as ever . . . . ☐

11. I feel restless as if I have to be on the move
- Very much indeed . . . . . ☐
- Quite a lot. . . . . ☐
- Not very much. . . . . ☐
- Not at all . . . . . ☐

12. I look forward with enjoyment to things
- As much as ever I did . . . . . ☐
- Rather less than I used to . . . . . ☐
- Definitely less than I used to . . . . . ☐
- Hardly at all . . . . . ☐

13. I get sudden feeling of panic
- Very often indeed . . . . . ☐
- Quite often . . . . . ☐
- Not very often . . . . . ☐
- Not at all . . . . . ☐

14. I can enjoy a good book or radio or TV programme
- Often . . . . . ☐
- Sometimes . . . . . ☐
- Not Often. . . . . ☐
- Very seldom . . . . . ☐

For Office use only:
Total odd = Ax _____ Total even = De _____

Appendix M: SEALS questionnaire.

MF 18

SEALS Inventory

Today's date: ___ ___ ___
dd mm yy

Please answer every question: ✓one

In the last week:		**Many times**	**Some-times**	**Occasio-nally**
1	Have you felt enthusiastic about doing things?	☐	☐	☐
2	Have you felt like nodding off to sleep during the day?	☐	☐	☐
3	Have you been irritable with people?	☐	☐	☐
4	Have you felt too tired to do anything at all in the evenings?	☐	☐	☐
5	Have you let other people make your mind up for you?	☐	☐	☐
6	Have you felt alert even when on your own?	☐	☐	☐
7	Have you fallen asleep during the day without meaning to?	☐	☐	☐
8	Have you felt satisfied?	☐	☐	☐
9	Have you thought a lot about problems you may have?	☐	☐	☐
10	Have you been even-tempered?	☐	☐	☐
11	Have you been as affectionate towards other people as you would have liked?	☐	☐	☐
12	Have you been involved in rows or arguments at home?	☐	☐	☐

CO

MF 18

SEALS Inventory

In the last week:		✓ one: Many times	Some-times	Occas nally
13	Have you had to make lists or notes to remind you to do things?	☐	☐	☐
14	Have you had to give up something because of difficulty concentrating?	☐	☐	☐
15	Have you been worrying about your future?	☐	☐	☐
16	Have you found it difficult to join in when you have been with other people?	☐	☐	☐
17	Have you stayed awake later than usual?	☐	☐	☐
18	Have you felt you couldn't be bothered to do things?	☐	☐	☐
19	Have you got on as well as you would like with people close to you?	☐	☐	☐
20	Have you fallen asleep before going to bed?	☐	☐	☐
21	Have you planned to do something but then forgotten?	☐	☐	☐
22	Have you found it difficult to enjoy yourself?	☐	☐	☐
23	Have you found it difficult to follow the story of a TV programme, newspaper article, etc.?	☐	☐	☐
24	Has anyone had to tell you something twice because you forgot it the first time?	☐	☐	☐

MF 8

SEALS Inventory

In the last week:		✓ one Many times	Some-times	Occasio nally
25	Have you had to do things very slowly in order to get them right?	☐	☐	☐
26	Have you felt fuzzy headed or vague?	☐	☐	☐
27	Have you gone to bed earlier than you usually do?	☐	☐	☐
28	Have you had any difficulty following what people were saying?	☐	☐	☐
29	Have you shouted or yelled for very little reason?	☐	☐	☐
30	Have you found it easy to enjoy yourself?	☐	☐	☐
31	Have you been worrying about your family's future?	☐	☐	☐
32	Have you felt slowed up?	☐	☐	☐
33	Have you avoided mixing with people?	☐	☐	☐
34	Have you lost your temper?	☐	☐	☐
35	Have you felt slowed up or dulled even in the company of other people?	☐	☐	☐
36	Have other people had to make decisions for you?	☐	☐	☐
37	Have you had a lot to say to people?	☐	☐	☐
38	Have you forgotten where you've put things?	☐	☐	☐

Appendix N: IPQ

Version P

ID:

ILLNESS PERCEPTION QUESTIONNAIRE

Please indicate how frequently you now experience the following symptoms as part of your condition:

Illness Identity

	All of the time	**Frequently**	**Occasionally**	**Never**
Pain	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Breathlessness	☐	☐	☐	☐
Weight Loss	☐	☐	☐	☐
Fatigue	☐	☐	☐	☐
Stiff Joints	☐	☐	☐	☐
Sore Eyes	☐	☐	☐	☐
Headaches	☐	☐	☐	☐
Upset Stomach	☐	☐	☐	☐
Sleep Difficulties	☐	☐	☐	☐
Dizziness	☐	☐	☐	☐
Loss of Strength	☐	☐	☐	☐

Version P

We are interested in your own personal views of how you now see your condition. Please indicate how much you agree or disagree with the following statements about your condition.

Cause	Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree
A germ or virus caused my condition	☐	☐	☐	☐	☐
Diet played a major role in causing my condition	☐	☐	☐	☐	☐
Pollution of the environment caused my condition	☐	☐	☐	☐	☐
My condition is hereditary - it runs in my family	☐	☐	☐	☐	☐
It was just by chance that I developed this condition	☐	☐	☐	☐	☐
Stress was a major factor in causing my condition	☐	☐	☐	☐	☐
My condition is largely due to my own behaviour	☐	☐	☐	☐	☐
Other people played a large role in causing my condition	☐	☐	☐	☐	☐
My condition was caused by poor medical care in the past	☐	☐	☐	☐	☐
My state of mind played a major part in causing my condition	☐	☐	☐	☐	☐

Version P

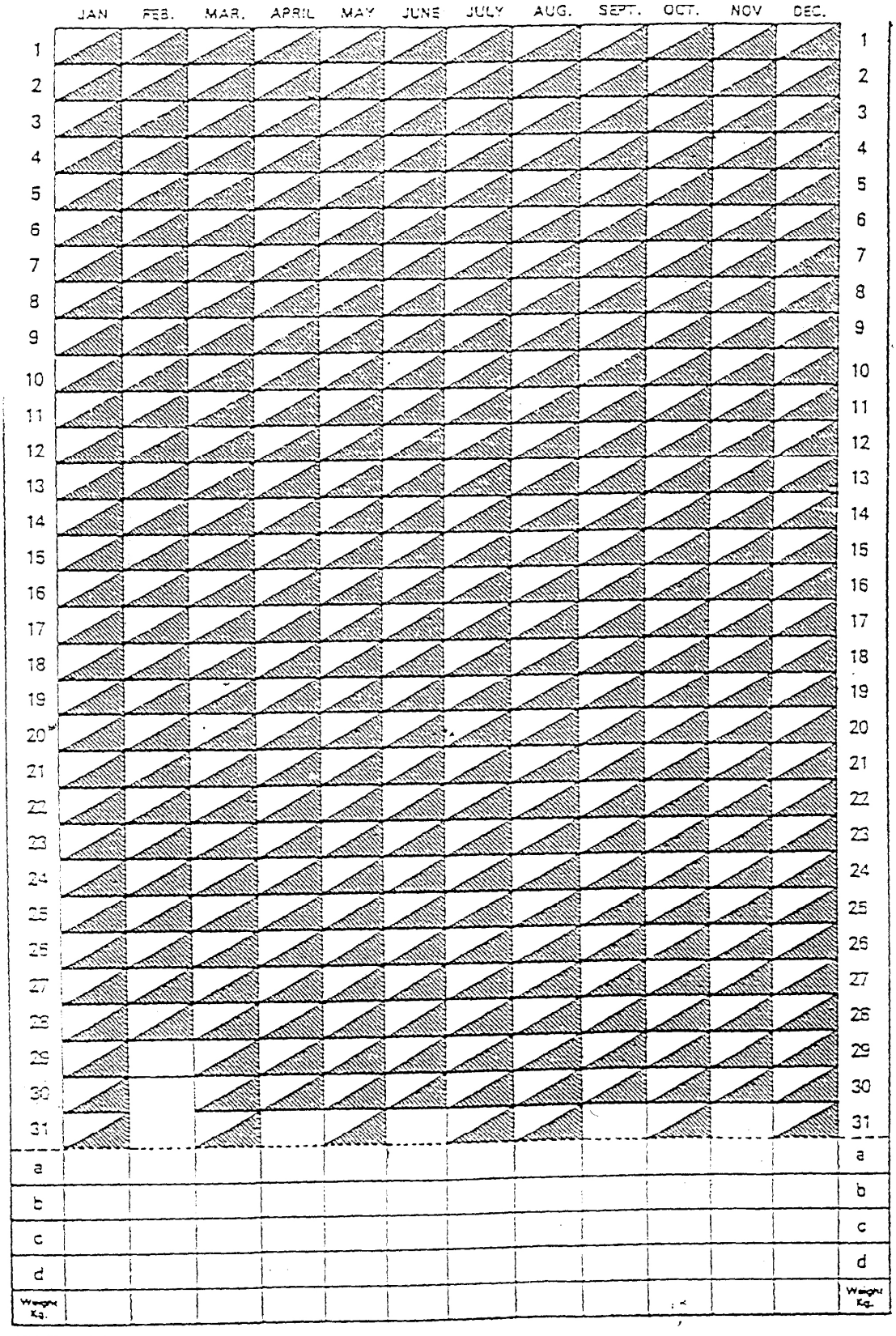
Time-line	**Strongly Agree**	**Agree**	**Neither Agree nor Disagree**	**Disagree**	**Strongly Disagree**
My condition will last a short time	☐	☐	☐	☐	☐
My condition is likely to be permanent rather than temporary	☐	☐	☐	☐	☐
My condition will last for a long time	☐	☐	☐	☐	☐

Consequences	**Strongly Agree**	**Agree**	**Neither Agree nor Disagree**	**Disagree**	**Strongly Disagree**
My condition is a serious one	☐	☐	☐	☐	☐
My condition has had major consequences on my life	☐	☐	☐	☐	☐
My condition has become easier to live with	☐	☐	☐	☐	☐
My condition has not had much effect on my life	☐	☐	☐	☐	☐
My condition has strongly affected the way others see me	☐	☐	☐	☐	☐
My condition has serious economic and financial consequences	☐	☐	☐	☐	☐
My condition has strongly affected the way I see myself as a person	☐	☐	☐	☐	☐

Version P

Control/Cure	Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree
My condition will improve in time	☐	☐	☐	☐	☐
There is a lot which I can do to control my symptoms	☐	☐	☐	☐	☐
There is very little that can be done to improve my condition	☐	☐	☐	☐	☐
My treatment will be effective in curing my condition	☐	☐	☐	☐	☐
Recovery from my condition is largely dependent on chance or fate	☐	☐	☐	☐	☐
What I do can determine whether my condition gets better or worse	☐	☐	☐	☐	☐

Appendix O: Attack diary



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