SLEEP DISTURBANCE

IN

MULTIPLE SCLEROSIS

Paula Cowan BSC

Leeds Metropolitan University, Faculty of Health and Environment,

School of Health and Human Sciences

This thesis is submitted as fulfilment of the requirements for the award of Masters of Science in Multiple sclerosis

August 2009

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ACKNOWLEDGEMENTS

Liz Mackay my tutor from Leeds Metropolitan University for her encouragement and advice.

I would like to thank my sister Fiona for her endless patience and support (and a shoulder to cry on!!) and my brother- in- law John.

I would also like to thank Professor Tom Mercer at Queen Margaret University for his support and precious time.

My Boss Beverley Bryan for providing study leave and support throughout the long slog!

My thanks also go to Belinda Weller (Consultant Neurologist) who supported me with this project.

To all friends and family who were patient and put up with my grumps as the deadline came closer.

ABSTRACT

Introduction: To study sleep disturbance in patients with multiple sclerosis (MS) and its potential relationship to fatigue and other variables.

Method: 30 patients with MS completed the Fatigue severity scale (FSS), Modified Fatigue Impact scale (MFIS), Pittsburgh Sleep Quality Index (PSQI) and the Hospital anxiety and depression (HADS) scales. All patients were relapse and co-morbidity free. Expanded Disability Status Scale (EDSS) was recorded with other demographics.

Results: More than half of the participants studied showed sleep impairment (63.3%). There was a significant difference in HADS scores between the 2 groups (PSQI ≤5; no clinical sleep impairment and >5 clinical sleep impairment), p= 0.037 and also a trend towards significance for MFIS, p=0.097. MFIS cognitive fatigue subscale was the principal factor explaining this trend towards significant difference (p= 0.094). There were no significant differences in scores for EDSS and FSS. There was a positive correlation between HADS & MFIS global score rho=0.5, R_2=0.25, n=30, p=0.005 and also HADS & MFIS Cognitive subscale score, rho=0.6, R_2= 0.36, n=30, p= 0.000.

The most commonly reported causes of sleep impairment were pain, feeling too hot and nocturia.

Conclusions: Sleep impairment is becoming more recognised as a problem for people with MS. The symptoms associated with poor sleep may well be treatable; however the underlying cause of sleep disturbance is still unknown and is likely to be multifactorial. Sleep disturbance appears to be an important contributing factor to fatigue in patients with MS and in particular impacts cognitive fatigue. This may form a cycle of symptoms including increased depression. Sleep disturbance and its causal factors is an exciting area both for researchers and health professionals involved in the treatment of patients with MS.

1 INTRODUCTION

1.1 Background

Multiple Sclerosis (MS) is a chronic demyelinating disease of the central nervous system and is the third most common cause of neurological disability in adults between 20-50 years of age (Dombovy, 1998).

An estimated 10,500 people in Scotland live with MS; no other country exceeds this prevalence per capita. The reasons for this are at present unknown. (MS Society Scotland, 2008). Although the aetiology of multiple sclerosis (MS) is unclear, accumulating evidence suggests that MS is the result of gene-environment interactions and that environmental factors are of primary importance in initiating the disease process (Jin et al., 2003).

1.2 Clinical features of MS

Symptomatology of MS has been reported to be very complex in nature due to the diverse locations of the central nervous system (CNS) lesions in individual patients. Symptoms can range from mild sensory loss to severe spasticity and weakness. In addition to the complexity of the symptoms of MS, the course of the disease varies within individuals; this variation is reflected in the internationally standardised clinical subtypes described by Lubin & Reingold (1996) in Figure 1:

Figure 1: International Clinical Subtypes of MS

Relapsing remitting (RR): Clearly defined disease relapses with full recovery or with sequelae and residual deficit upon recovery. Periods between disease relapses are characterised by a lack of disease progression.

Secondary progressive (SP): Initial RR disease course followed by progression with or without occasional relapses, minor remissions and plateaus.

Primary progressive (PP): Disease progression from onset with occasional plateaus and temporary minor improvements.

There is still a huge uncertainty about this disease the implications of which will now be discussed.

1.3 Intervention for MS

MS usually starts in early adult life and the current lack of a cure means that symptom management to improve quality of life is the typical focus of treatment (Davis, 2005). Davis (2005) has grouped symptoms of MS into three general areas (see figure 2):

Figure 2: Classification of Symptoms, Davis 2005

Primary symptoms are those that manifest due to actual demyelination within the CNS such as spasticity, ataxia, weakness and tremor.

Secondary symptoms are symptoms that manifest due to the presence of primary symptoms and include contractures, pressure sores, osteoporosis and infections.

Tertiary symptoms stem from the psychological stress related to having a chronic disease.

To date primary symptoms have mostly been treated by the use of intervention models which base treatment on the individual patient's neurological function and behaviour (Davis, 2005). However, in clinical practice, secondary and tertiary symptoms tend not always to be considered or indeed treated in the MS population. One such symptom which is becoming more evident in this population is sleep disturbance (Davis, 2005). Sleep disturbance may fit into the category of secondary or tertiary symptoms depending on the underlying cause. Sleep disturbance has also been subcategorised by Davis (2005) as an invisible symptom along with fatigue, cognitive problems and sensory disturbance, all of which are common in MS. Invisible symptoms are defined as those symptoms that are life limiting but not readily discernible to others (Davis, 2005).

White et al., (2008) found in their study that invisible symptoms, such as sleep disturbance, were associated with greater health distress compared to visible ones. The study carried out by White et al., (2008) included a random sample of 200

participants and utilised validated questionnaires. The results of this study are therefore credible and provide a starting point for health professionals to begin to identify and address these invisible symptoms.

The National Institute for Clinical Excellence (NICE) guidelines on the treatment of multiple sclerosis (NICE, 2003) recommends that all persons with MS have options to receive treatments that may improve symptoms and hence improve quality of life. The differing disease course of MS requires therapeutic options to be sensitive to the type of MS that the patient presents with. The Scottish Government paper 'Better health, better care' (2008) proposes to encourage patients to be actively involved in self management, this philosophy is also reflected in the Department of Health initiative for "managing long term conditions" (DoH, 2009). The recommendations from both these reports advise practitioners to facilitate patients to be more proactive and engaged in their own disease management. These government targets when translated for clients with MS should lead clinical practitioners into providing more timely information and support. This type of intervention empowers the client to be actively involved in their own treatment and increase their depth of understanding of the disease that they are living with (DoH, 2009).

Self management could be introduced at all levels of symptoms but within this study the focus will be sleep disturbance as a secondary or tertiary symptom.

1.4 Psychosocial implications of MS

For many people, receiving a diagnosis of multiple sclerosis (MS) is highly stressful. The disease can pose major challenges and obstacles in terms of employment, sexual relations, family functioning and activities of everyday living (McNulty, Livneth & Wilson, 2004). McNulty, et al., (2004) reported that the onset of a physical disability invariably triggers a chain of psychological reactions in the affected individual. Some of the reactions that have been reported include: aggression, anger, apprehension, anxiety, denial, emotional lability, dependency, euphoria, helplessness and hopelessness. (Dalos, et al., 1983; Rabins, et al., 1986; Montel & Bungener, 2007).

The psychosocial functioning of patients with MS has been compared with other neurological disorders and findings suggest that patients with MS express more

variability in their reactions to the disease and more intense depressive reactions (Dalos, et al., 1983; LaRocca, 1984).

As early as 1977, Matson and Brookes noted that adaptation to MS requires not only an initial adjustment to the diagnosis of the condition, but also continuous efforts of readjustment due to the erratic nature of the symptoms. In more recent literature, Mullins et al., (2001) reported that for a chronic disease like MS there may be continual stress due to the course of the disease being largely unpredictable. Uncertainty is described by Devins & Shnek (2000) as a prominent source of stress, placing the individual with MS at increased risk of emotional difficulties.

Mohr (2007) further discussed that because of the possible impact of stressful events on MS disease onset and exacerbation, understanding factors that mitigate or exacerbate stress in MS appears critical.

1.5 Sleep disturbance in MS

Clinical experience has highlighted that sleep disturbance in multiple sclerosis (MS) is reported regularly in outpatient clinics by patients with MS. However to date there has been a lack of evidence in terms of research within this area of sleep disturbance and MS. Literature that mentions sleep disturbance in MS is found in the topic of fatigue where it is cited as being an important secondary cause of fatigue (Krubb, 2003).

Sleep disturbance is reported by Lobentanz et al., (2004) as adversely affecting the quality of life of the person with MS and to date there is insufficient research to inform clinical practice of the direction any intervention should take.

This study will investigate sleep disturbance in order to add to current literature and potentially provide further insight as to how this symptom can be improved.

2 LITERATURE REVIEW

2.1 Introduction

A literature search was conducted on Medline, CINAHL, Embase and the Cochrane databases covering 1966-March 2009. Further papers were obtained from hand searches of relevant journals and abstract books of conference proceedings.

Keywords used were 'Multiple sclerosis', 'sleep', 'sleep disturbance', 'normal sleep', 'fatigue', 'depression', 'cognition', 'nocturia', 'restless leg syndrome', 'spasm'. Searches were limited to English language.

The following literature review consists of three sections one of which is further subdivided:

- Sleep disturbance in the normal population.
- Sleep disturbance and MS- divided into three subsections: frequency of sleep disturbance in MS, causes of sleep disturbance in MS and fatigue and sleep disturbance in MS.
- Conclusions; a summary of the main points from the above literature search.

2.2 Sleep disturbance in the normal population

Sleep was described by Stores, (2009), as a state of rest normally occurring in a recumbent position, quietly with little movement, during which consciousness and responsiveness are decreased. This state was reported by Stores, (2009) as being reversible by either external stimulation or internal satiation.

Studies have shown that difficulty sleeping (insomnia) is reasonably common in the general population. For example, Novak et al., (2008) carried out a study incorporating a large sample of 12000 adults which involved door to door investigations using validated questionnaires to investigate sleep in normal population of adults. Novak et al., (2008) extrapolated from his study that in the general population 10% of adults have chronic insomnia.

A similar study was carried out by Montgomery & Dennis in 2009, the author's reported that in the general population the most common types of sleep problems

reported are insomnia (both in initiating and maintaining sleep) and early morning waking with an inability to return to sleep. Older adults primarily report difficulty in maintaining sleep (Montgomery & Dennis, 2009).

Montgomery and Dennis in 2009 also noted that the prevalence of sleep problems in adulthood increases with age. They further state that while not all sleep changes are pathological in later life, severe disturbances in sleep may lead to: depression, cognitive impairments, deterioration of quality of life with resultant stresses for carers and ultimately increased healthcare costs.

Studies on the effect of gender on the sleep patterns in humans are limited. Reports are based on small samples (30 or less) of select populations (Bliwise & Young, 2007; Roehrs, et al., 2006), with two recent publications based on the general population of the Sleep Heart Health Study (SHHS) (Redline et al., 2004; Walsleben et al., 2004). The latter two studies demonstrated that women, in general, sleep better than men. However, one limitation of the studies was that they did not include a wide age range, primarily focusing on middle-aged and older individuals. In contrast to the frequent subjective complaints of disturbed sleep by women entering the menopause phase of life (Kravitz et al., 2003; Kuh et al., 1997; Matthews et al., 1990; Young et al., 2003), there have been two studies that reported no effects of menopause and hormone treatment (HT) on objective sleep patterns (Shahar et al., 2003; Young et al., 2003).

Sleep disturbance has been seen to affect both mental and physical health (Drake et al., 2003). This relationship has been established through large-scale epidemiological studies of normal sleep and clinical studies documenting the adverse health consequences of disordered sleep (Drake et al., 2003; Reid et al., 2006; Bliwise & Young, 2007).

Frank in (2006) has reported that sleep is for the brain rather than the body and promotes brain plasticity. The neural process most impacted by sleep according to Frank (2006), is cognition. Chaudhuri & O'Behan (2004) have shown that structural lesions of neural pathways interconnecting the basal ganglia, thalamus, limbic system and higher cortical regions are implicated in the pathophysiology of central fatigue and Pace-Schott & Hobson (2002) take this further to say that some of these networks also regulate sleep and wake. The most common treatment for sleep disorders (particularly

insomnia) is pharmacological (Montgomery, 2002). Those who receive treatment typically receive benzodiazepines, which have known side effects including tolerance, addiction, daytime sedation, associated falls, hip fractures, and car accidents (Montgomery, 2002). Thus, the benefits of such treatment may be outweighed by the potential costs.

2.3 Sleep disturbance and MS

2.3.1 Frequency of sleep disturbance in MS

Clark et al., (1992), reported that MS patients are three times more likely to experience sleep difficulties than healthy controls. However this is likely to be an underestimate as their study only included MS patients who were in remission. More recently, Lobentanz et al., (2004) concluded that In addition to experiencing more frequent disturbed sleep, people with MS are twice as likely to experience reduced sleep quality (Lobentanz et al., 2004). However, in this study Lobentanz et al., (2004) selected their sample from members of the local MS society (introducing a limitation to the study in terms of sample selection), the implications of this being that it may be inappropriate to generalise to the wider MS community. Lobentanz et al., (2004) started their study with 1000 participants but in reality only 250 fully completed the questionnaires, again limiting the ability to generalise to the population. Lobentanz et al., (2004) looked at different factors impacting quality of life in a group of MS patients and found sleep disturbance, fatigue and depression all to be frequent factors (percentages were not given). The interrelationship however was not investigated. Furthermore the quality of life questionnaire used was the Quality of life index, which does not have items directly related to fatigue or sleep.

A more recent study by Stanton, Barnes & Silber, (2006) involved a moderate sample of sixty outpatients with MS. In the study they began to explore the nature and frequency of sleep disturbance in MS and reported that fatigue and excessive daytime sleepiness were common in their study group (32%), as was sleep disturbance (>50%). Stanton et al., (2006) designed their own sleep diary (non-validated) for the purpose of the study. The use of this diary allowed qualitative information to be collected and hence allowed the study population to describe their sleep experiences. This included

being able to report time spent in bed, causes of night time awakenings and afternoon naps. It however did not allow calculations of how much time was actually spent asleep. With their sample of 60 participants they concluded that more than half (an exact percentage was not given) of the patients reported sleep problems (including falling asleep, waking during the night and early wakening) on two or more nights within a week. The study lacked a healthy control group which reduced the ability to predict that the sleep problems described were more common than those seen in the general population.

Of the limited studies available it seems that sleep disturbance does appear to be more common in MS however there is still a lack of robust evidence to fully support this claim.

2.3.2 Causes of sleep disturbance in MS

Tachibana et al., in 1994, reported that patients with MS had sleep disorders due to restless legs syndrome (RLS) and periodic limb movement disrupting it. Other disturbances recorded included spasms, snoring and nocturia. Their study had only 28 patients with no control and one participant was going through an active relapse at the time of the study. During a relapse patient symptoms are heightened and hence may skew results (Vukusik & Confavreux, 2007). All participants were inpatients hence had been admitted for acute problems of various descriptions which may alter normal symptoms. Ten had been admitted for steroid treatment which causes insomnia. Their sleep was monitored during their time in hospital hence not representative of their normal sleeping habit. They did however use a questionnaire to look at sleep history but subjective scale can be affected by mood or memory (Blaxter, Hughes & Tight, 2008). The study by Tachibana et al., (1994) therefore would need to be more robust in terms of standardisation, a wider population and exclude conditions that would skew results.

An earlier study by Taphoorn et al., (1993) did not show a relationship between sleep disorders and restless leg syndrome. Their study consisted of only 16 participants and no control group and used outpatients in the study. The two studies are not comparable.

In 1992, Clark et al., examined 10 questions relating to sleep on the Minnesota Multiphasic Personality Inventory (MMPI) in a highly selected group (i.e. age less than 50, no medication, ambulant, RR course, no co morbidity) of outpatients with MS. The method of this study was not clear and no description of the battery of tests was given. Patients reported sleep problems 3 times more frequently than controls. In this study they claimed that the presence of sleep disturbance was related to lesion site of the disease. They highlighted the right and left frontal supraventricular white matter and the deep white matter of the right insula. It was speculation on the part of the researchers in this study that depending on the site of the lesion this may cause primary symptoms like e.g. restless legs which in turn disrupt sleep. However, this knowledge may have implications for the diagnosis of sleep problems and therefore treatment strategies and if true and would warrant further research.

More recently Fleming et al., (2005) reviewed the literature to find causes of sleep disturbance in MS and reported that 50% of patients with MS describe pain as a significant problem in relation to sleep disturbance. This review was very poorly reported in terms of total number of papers, type of research and presented as a list rather than a critical review. It listed papers under causes of sleep disturbance, those being: depression, RLS, pain, medication and nocturia. It however gave the reader further papers to explore.

Rae-Grant et al., (1999) did a survey of 224 patients with MS and a comparable control group to investigate symptoms in MS. They described that pain was present in 79% which can be burning (neuropathic) or cramping (spastic) and can limit the patient's ability to deal with anxiety and depression all of which have the potential to disrupt sleep. They also found fatigue to be present in 67% of patients (17% in controls) and RLS in 53% compared to 14% in controls.

Other causes of sleep disturbance in MS which have been suggested are; nocturia, medication effect and depression (Ford & Kamerow, 1989).

Nocturia affects 70-80% of patients with MS (Araki et al. 2002) and can lead to repeated awakenings and sleep disruption (Araki et al., 2002; Leo et al., 1991; Tachibana et al., 1994).

Leo, Rao & Bernardin, (1991) surveyed 47 patients with MS and 63 matched controls. Correlational analysis demonstrated an increased frequency of nocturnal awakenings, prolonged sleep latency and early morning awakenings caused by bladder spasticity in these patients. Although a relatively small sample, they also found that increased nocturnal awakenings were associated with increased daytime fatigue.

Depression was investigated by Fruehwald et al., (2001) with 60 Ms patients in an outpatient clinic and 60 healthy controls using standardised questionnaires. Limiting the sample to an outpatient setting would exclude acute suffering and the patients were all mainly early diagnosed with very little disability (EDSS <4) but in this select group they found depression to be the greatest predictor of quality of life with the potential to cause insomnia.

In summary the main causes of sleep disturbance that seem to be highlighted in literature are restless leg syndrome, nocturia, pain and depression. Some of which may be secondary to lesion site of the MS. Studies are few and limited to small sample size with select participants therefore not representing the population of MS.

2.3.3 Fatigue and sleep disturbance in MS

Fatigue is reported by about 70% of people with multiple sclerosis (MS) and has been linked in some recent studies to sleep disturbance (Krubb, 2003). Fatigue is a major source of disability and is commonly reported as being a primary cause of disability in MS (Bakshi, 2003; Krubb, 2003). Fatigue can have primary (direct) and secondary (indirect) causes. A direct cause has been suggested as due to the lack of myelin sheath in MS (Krubb, 2003), whereas an indirect cause could be due to something like sleep disturbance. Both Bakshi (2003) and Krubb (2003) recommend identifying the indirect causes and intervening accordingly because to date there is no strong evidence to support treatment of the direct causes.

MS fatigue, being an invisible symptom, is often not identified in routine neurological assessments therefore intervention may not routinely happen. Where it is recognised it is not always managed effectively in terms of appropriate treatments because of its subjective nature (Flensner & Soderhamn, 2003). Fatigue can be a major source of disablement, interfering with usual and desired activities, reducing cognitive

performance (memory, concentration) and is often reported by patients as being amongst their most severe and distressing symptoms (Fisk et al., 1994; Krupp, 2003). It therefore can have a dramatic effect on quality of life. When fatigue is perceived as causing restrictions and limitations on daily life, it may interfere with the accomplishment of the individual's most important goals, which, in turn, may contribute to an emotional state where the individual does not experience good health (Flensner & Soderhamn, 2008).

Improving sleep may have an impact on fatigue thereby positively impacting quality of life (Attarian, et al., 2004).

Attarian et al., (2004) looked at a very small study of 15 MS clients. The objectives of this study were to determine whether circadian rhythm abnormalities and/or disturbance of sleep exists in patients with MS and if they correlate with fatigue and excessive daytime sleepiness as assessed by standardised questionnaires. The method involved three groups of subjects; those with MS, who had fatigue; MS patients without fatigue; and healthy volunteers. The groups were comparable in terms of demographics. Results showed a significantly high probability of a relationship between fatigue and disrupted sleep or abnormal sleep cycles (fisher exact test, $p=0.003$). The authors concluded that the sleep abnormalities may be playing a role in the pathophysiology of MS fatigue. The actigraph method used in this study does not indicate the cause of sleep disruptions and also in this study patients were relapsing-remitting and/or secondary progressive and disease modifying treatments were not discontinued.

In contrast to this, Taphoorn, et al., (1993) used 16 MS patients with prominent complaints of fatigue and sleep disorder, in a similar study and found no difference in scores for actigraph and no evidence of circadian rhythm disturbances. These contrasting results may be attributable to the fact that the studies included patients with different disease forms, relapsing remitting and chronic progressive, in active and non-active disease-state and did not account for the influence of drugs and also for other confounding variables such as depression that may impact on fatigue.

Kaynak et al., (2006) investigated the presence of sleep disturbance to see if it related to fatigue by using objective and subjective measures and was the first study which

evaluated both macro and microstructure of sleep. Macrostructure was defined as duration, continuity, latencies, wake time etc and microstructure was defined as arousals occurring spontaneously or associated with movements or respiratory events. They found fatigue could be partially explained by disruption of sleep microstructure. The disruption of sleep microstructure has the potential to cause no refreshing sleep and poor subjective sleep quality. This was shown to be the case in this study with much higher subjective scores for MS patients. They concluded that MS causes sleep fragmentation in terms of both macro and microstructure. It has to be noted that this study had only 27 MS patients with fatigue and only 10 without fatigue and 13 control subjects therefore difficult to translate to population.

2.4 Conclusions

There is emerging literature in the areas of; nature, cause and implications of sleep disturbance in MS, however this is limited. The limited numbers of studies to date have not been sufficiently robust in design and have been limited in the majority by small study groups.

About 70% of patients with multiple sclerosis complain of general fatigue and more than 50% of MS patients, when asked about their quality of sleep report that their sleep is inadequate (Boggild, 2005).

Strober et al., (2005) investigated the relationship between depression, sleep and fatigue and concluded that all three were significant independent contributors to fatigue in MS, but sleep disturbance was the best predictor.

Sleep disturbance can potentially increase disease impact and is associated with poorer mental health, lower work productivity and higher utilisation of health care services (Manocchia, Keller & Ware, 2001). Sleep disturbance is an area of care for MS patients which requires current practice to be extended in order to support and understand this need.

This study will allow the topic of sleep disturbance to be explored further and may begin to show its prevalence and its correlation to various factors.

3 AIMS AND HYPOTHESES

3.1 Aims

Aim 1: To study the relationship between sleep disturbance and fatigue in a group of patients with multiple sclerosis.

Table 1: Hypotheses 1&2

H1	There is a statistically significant difference between MFIS scores in a group of patients with (PSQI score ≤5) and without (PSQI score >5) sleep disturbance.
Ho1	There is no statistically significant difference between MFIS scores in a group of patients with (PSQI score ≤5) and without (PSQI score >5) sleep disturbance.
H2	There is a statistically significant difference between FSS scores in a group of patients with (PSQI score ≤5) and without (PSQI score >5) sleep disturbance.
Ho2	There is no statistically significant difference between FSS scores in a group of patients with (PSQI score ≤5) and without (PSQI score >5) sleep disturbance.

Aim 2: To study the relationship between sleep disturbance and disability.

Table 2: Hypothesis 3

H3	There is a statistically significant difference between EDSS scores in a group of patients with (PSQI score ≤5) and without (PSQI score >5) sleep disturbance.
Ho3	There is no statistically significant difference between EDSS scores in a group of patients with (PSQI score ≤5) and without (PSQI score >5) sleep disturbance.

Aim 3: To study the relationship between sleep disturbance and anxiety/ depression.

Table 3: Hypothesis 4

H4	There is a statistically significant difference between HAD scores in a group of ms patients with (PSQI score ≤5) and without (PSQI score >5) sleep disturbance.
Ho4	There is no statistically significant difference between HAD scores in a group of ms patients with (PSQI score ≤5) and without (PSQI score >5) sleep disturbance.

3.2 Objectives

1. To increase awareness of sleep disturbance in ms with health care professionals.
2. Gain a deeper understanding of sleep disturbance in MS.
3. To outline potential interventions to improve sleep disturbance in MS.

4 METHODOLOGY

4.1 Introduction/research design

This is a descriptive, cross-sectional, correlational design using quantitative data. Quantitative research is empirical research where the data are in the format of numbers (Blaxter, Hughes & Tight, 2008).

A descriptive design was used because it would describe the situation as it occurs without any intervention, which allows the researcher to gain information about the participants on what occurs naturally in the 'real life' situation (Drummond, 1996). The intention being to discover information about sleep, fatigue and depression as it is for the patients currently without intervention. Descriptive studies are also important for identifying problems in practice, for justifying current practise and developing theory (Burns & Grove, 1987). In other words this may help to look at the current service and highlight any short comings with the potential to improve.

A correlation design was chosen to concentrate on relationships i.e. the relationship between fatigue, sleep and anxiety/depression, not to mention other demographic factors where appropriate. The situation will be studied in search of associations and links. Once observed and recorded, the resulting patterns and relationships can be analysed and clarified. The researcher is also looking back over a very short time scale in this case at past information e.g. what was your sleep like last week? Or over the past week how was your fatigue? In this type of study information can be gathered quickly which has an advantage for the limited time scale for submission of the thesis, however one disadvantage is that memories may be distorted and cannot be checked (Tod, 2006).

The cross-sectional design in this study attempts to measure cause and effect while focusing on things that are happening simultaneously. This design does allow results to be obtained quickly and is cost-effective to carry out which is a benefit in the current climate of recession. The cross sectional design is particularly useful when an investigator is taking a preliminary look at a problem. In this case looking at whether sleep disturbance is a problem and what it may cause in terms of effects on the patient. It can only provide suggestive evidence therefore.

4.2 Validity and reliability

Instruments that were already developed were chosen for this study, namely fatigue severity scale (FSS) (see appendix 6), Modified fatigue impact scale (MFIS) (see appendix 7), Pittsburgh sleep quality index (PSQI) (see appendix 5) and the Hospital anxiety and depression scale (HADS) (see appendix 8), this proved efficient in terms of time and development costs.

Developed instruments are generally buttressed by evidence of reliability and validity; the investigator can thus be more certain of their results (Blaxter, Hughs & Tight, 2008). If an instrument is unreliable it cannot measure variation across subjects. Reliability has been described as when repeated measurements on the same person should result in similar outcomes each time (Tod, 2006). If a measure has acceptable reliability then it is necessary to check out psychometric properties to see if it is also a valid measure of that which it is supposed to be measuring. The four questionnaires mentioned were used to gather quantitative data three of which used a Likert type scale and one used a self reported items scale. Likert scales can be open to bias which could be induced by people who are inclined to agree or disagree with any written statement or who tend to avoid making decisions (Drummond, 1996).

Each measure was reviewed for: validity and reliability; time necessary to administer; training in order to carry out test; scoring method; whether it was widely used for comparison and reported as follows:

4.3 Measures to be used

The following scales were selected, reviewed and found appropriate for this study:

1. **Fatigue Severity Scale** (FSS) (see APPENDIX 6). This is a nine-item self reported Likert scale with 7 levels of agreement with each statement. It is a widely recognised scale for measuring the severity of fatigue over the past week (Krupp et al.,1989; Schwartz et al.,1993). A direct measure of fatigue is essential for this study in order to look at the relationship with sleep. It is brief and easy to administer (takes 5 minutes), and demonstrates reliability and internal consistency. It was initially tested in two populations – MS and systemic lupus patients and was able to clearly differentiate the fatigue of these two diseases from that in the

normal population. The scale has good face validity and reasonable test-retest reliability. Valko et al., (2008) in their study with sample size of 200 found item analysis showing excellent internal consistency and reliability (Cronbach alpha= 0.93). It has been recommended that that Cronbach's coefficient alpha should be at least 0.60 for a self reported instrument to be reliable (Nunnally & Bernstein 1994). Patients with a mean score of 4 or more were defined as suffering from significant fatigue. (Krupp et al., 1989; Schwartz et al., 1993). Scoring is simple and done by adding up all the numbers circled.

2. **Modified Fatigue impact scale** (MFIS) (Fisk, 1994) (see APPENDIX 7).This is a 21 item Likert scale ranging from 0(no impact)-4 (almost always) with a maximum score of 84. It looks at the effects of fatigue on daily activity over the previous 4 weeks and is used to indicate the impact of fatigue on the patients' social, cognitive and physical status. Tellez, et al., (2005) correlated the FIS, MFIS and visual analogue of fatigue showing good criterion related validity. Kos et al., (2005) assessed the scales psychometric properties in 4 European countries and found no cultural or linguistic differences. It had good reproducibility (interclass correlation 0.84) and found cronbach's alpha 0.92, 0.88 and 0.92 for total score, the physical and cognitive subscales respectively, giving confidence to use it in research purposes. However the psychosocial subscale had a cronbach's alpha of 0.65 which would imply that it would be interpreted with caution. Completion only takes about 5-10 minutes and scoring is simple by adding a sum of all the numbers circled.

3. **Hospital anxiety and depression scale** (HAD) (see APPENDIX 8): Developed for the measurement of anxiety and depression (Zigmond *&* Snaith*, 1983).* It is a self-administered scale consisting of 14 polytomous items scored as two 7-item subscales for anxiety and depression and has shown to be valid and reliable for such. It is simple to use and takes 5 minutes to complete. Bjelland et al., (2002) did an extensive review of the literature for papers looking at validity and reliability of the HAD scale. This review incorporated 747 papers and was a follow on from an earlier review by Hermann (1997) of 220 papers that concluded that the HAD scale was a reliable and valid instrument for assessing anxiety and depression in medical

patients. This larger review by Bjelland et al., (2002) was felt necessary because the number of papers had increased fourfold and also included samples from the general population and looked at concurrent validity which Hermann's review did not. A mean Cronbachs alpha coefficient of internal consistency was 0.83 for the papers ranging from 0.69-0.90. Concurrent validity was found to range from good to very good in the papers reviewed. They concluded that the HAD scale was a reliable and valid measure for patients.

4. **Pittsburgh Sleep Quality Index** (PSQI) (Buysse, 1989) (see APPENDIX 5) it is a 19-item self report measuring problematic sleep. Higher scores reflect more sleep difficulties, and the instrument shows good sensitivity and specificity for identifying those with or without sleep impairments using a total score cut off of 5 (Cohen, 1988). The PSQI has internal consistency which was demonstrated in a sample of healthy control subjects (n=52), patients with sleep disorders (n=62) and depressed patients (n=34), and a reliability coefficient (Cronbach's Alpha) of 0.83 for the global score and test-retest reliability of 0.85 (Buysse, 1989). The PSQI can distinguish between people who have problems with sleep and a person who do not (validity) and has shown a sensitivity of 89.6% (Buysse, 1989). The PSQI has a global score which gives it an advantage of having a single overall assessment of sleep quality, and being simple to calculate, and allowing for direct comparisons. The PSQI is primarily intended to measure sleep quality and to identify good and bad sleepers, not to provide clinical diagnosis. It is not know whether the scale is useful for monitoring treatment response but for the purpose of this study this is not necessary. However responses to specific questions can point the clinician toward areas for further investigation (Buysse, 1989). Cole et al., (2007) did a literature review of current sleep measures and found only the PSQI to measure sleep latency which will be important within this study. It takes most patients 5-10 minutes to complete and scoring time is less than 5minutes.

These scales were contained within the one folder, clearly laid out in a typed format with consistent typeface for ease of filling them in and potentially reducing error.

The level of disability was assessed and recorded by the neurologist using the EDDS score (Kurtzke, 1989). The EDSS is the commonly accepted best outcome measure to evaluate disease progression in multiple sclerosis.

4.4 Recruitment/sample

The sample frame for this study was patients with MS who met the inclusion/exclusion criteria (see table 4).

The purpose of sampling is to acquire a sample that would accurately reflect the population under study (Tod, 2006).

For the purpose of this study consecutive sampling was chosen which allowed subjects to be taken from a list of out patients in the order in which they appeared on the list (Blaxter, Hughes & Tight, 2008). The participant group were selected from outpatient clinics with every patient attending the clinic having a chance of being selected. In order to reduce the effects of bias a neurologist (not the chief investigator) selected patients in terms of the inclusion/exclusion criteria. Done in this way you may or may not get a representative sample (Blaxter, Hughes & tight, 2008). However the outpatient clinic provides a service for patients at all stages of the disease process hence no group within this disorder are naturally excluded by selecting them from this clinic. The selected sample for this study will be broadly representative of most MS clients and will have the potential for generalisation across the MS population.

The exclusion criteria adopted (see table 4) meant that no participants fell within the statutory definition of Adults with Incapacity.

The study proceeded to recruit 30 patients within time constraints for the study to be completed and appropriate information disseminated. The study number has to be manageable in terms of time for analysis and collection (Crombie, 1997). Sample size is dependent on number of people who would be available and research design (Tod, 2006). The project took place over several weeks of clinic time (Monday and Wednesday mornings only) until the required sample size was met.

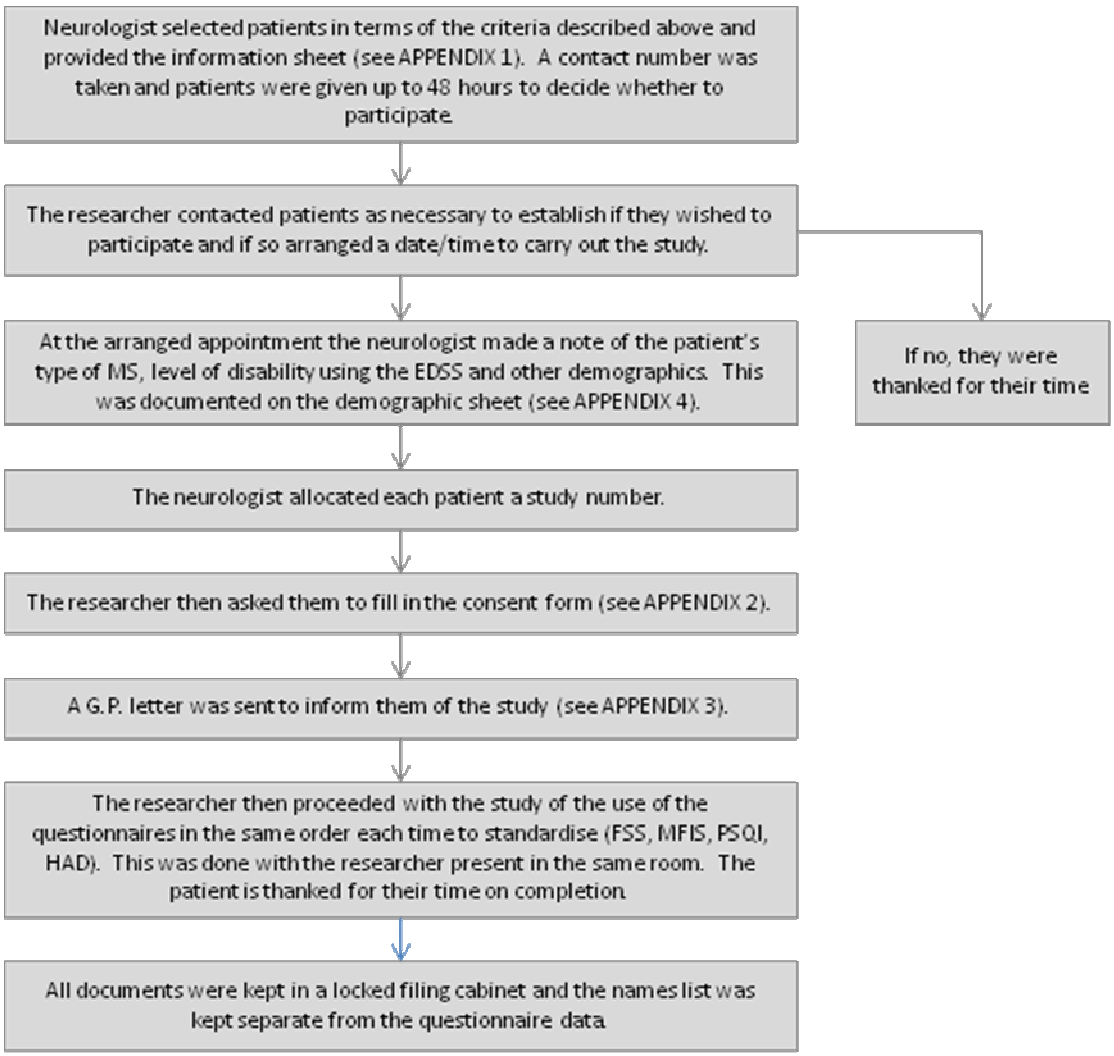
4.5 Participants

Table 4: Inclusion & Exclusion Criteria

Inclusion criteria	• Definitive diagnosis of multiple sclerosis as confirmed by the neurologist directly (McDonald et al 2004). • Ability to participate • Willingness to take part
Exclusion criteria	• Acute relapse because this temporarily increases and alters symptoms and hence would skew results (Leary et al 2005). • Co-morbid diagnosis of any other condition where sleep disturbance is a primary and common symptom e.g. clinical depression (Zetin & Hoepner, 2007). • Significant cognitive impairment precluding full participation in the study as assessed by the neurologist. Cognitive impairment includes language comprehension and expression problems in this context (Beins, 2004). • Co-morbid diagnosis of any other neurological disorder Eg head injured, stroke, dementia (Fleming & Pollak, 2005). • Those patients on medication for fatigue (Zifko, 2004). • Diagnosis of any other confounding factor due to the fact that this may alter the primary reason for sleep disturbance, giving other variables. • Refusal to participate for other reasons.

4.6 Data collection/procedure

The following flow chart shows the steps involved in data collection:



Face to face administering will improve return rates and reduce error by allowing patients to ask questions about items at the time of completion. It may also however introduce bias, but is essential due to time constraints and staff limitations. Bias will be reduced by standardising the instructions given to patients prior to completion (Blaxter, Hughes & Tight, 2008).

5 ETHICAL CONSIDERATIONS

5.1 Introduction

The key ethical considerations in conducting this research study related to the following as described by Beins (2004):

a. Consent

b. Anonymity and confidentiality

c. Personal safety of the researcher

d. Vulnerable study population

e. Clinician as researcher

f. Falsifying data

5.2 Consent

Approval was sought from the Lothian Research & Ethics Committee (see appendix 9) to carry out the study at the Western General Hospital, Edinburgh and also Management approval from the host site namely NHS Lothian (see appendix 10).

Informed consent was obtained from all participants after being given an appropriate time of at least 48 hours to consider participation and only after the patients had been given written information about the aims of the research, confidentiality and anonymity, and what it involves for the participant. The right to be informed also means that participants will be given a detailed but non-technical account of the nature and aims of research. Protecting patient, hospital, and physician confidentiality not only is ethical, but also protects from lawsuits should the project go on to be published (Byrne, 1998). This was ensured. The researcher explained to potential participants that involvement was voluntary and that they may withdraw from the research at any time, without any compromise to their usual healthcare.

5.3 Anonymity and confidentiality

As Patient confidentiality was essential all documents were kept within a locked filing cabinet within a locked room. The data produced by the study was not used for any

other use than that documented within the study information sheet. The client names list was kept separate from the analysis data which only contained a study number allocated by the neurologist to help limit bias during the analysis.

5.4 Personal safety of the researcher

The study will be carried out in the outpatient clinical area at all times. There was always a nurse specialist and a neurologist present if necessary. Support could also be sought from this team for reflection should an incident arise.

5.5 Vulnerable study population

The researcher appreciated that participants may be potentially vulnerable in this situation. To help manage emotionally challenging situations, the researcher will be sensitive and communicate empathy. If patients are identified as requiring physical or psychological support during the study, the patients can be directed to the nurse specialists or neurologist who will be in the clinical area at the time. Data collection took place in a consultation room in the neurological outpatient clinic which provided a confidential setting but also allowed the participants access to members of the MS team who could provide additional support if necessary.

5.6 Clinician as researcher

The researcher will attempt to avoid role conflict due to their clinical status by avoiding putting forward their own views and perspective. It will be important to avoid taking on the role of clinician and any health issues which arise will be directed towards the patient's healthcare team. Where a risk to the patient or someone else is revealed, the situation will be discussed with the patient's doctor or nurse.

5.7 Falsifying data

All steps will be taken to avoid fraud of any kind including; fabrication of data, figures designed to mislead the reader and plagiarism.

6 DATA ANALYSIS

Data analysis brings together statistical techniques and clinical experience: the statistics to show what is going on in the data and the clinical experience to make sense of the statistical findings (Crombie, 1997).

The use of questionnaires in this small-scale study allowed for a mixture of descriptive statistics and exploration of the inter-relationships between pairs of variables. Quantitative data was analysed using the software SPSS version 16 (statistical package for the social sciences). Software packages help with the process of analysing data but are not short cuts to rigorous analysis and still require the researcher to understand and interpret the results (Drummond, 1996). This will follow in the discussion.

Independent samples t-test was used for normally distributed continuous variables and the Mann-Whitney U test was used for continuous variables that were not normally distributed. Correlations between HAD score and MFIS scores were evaluated by means of Spearman correlation coefficients.

7 RESULTS

7.1 Introduction

Statistical information is presented in this section for relationships between the following variants:

- Sleep disturbance
- Fatigue
- Depression
- Disability

7.2 Participants

30 participants completed this study, of which 12 were male and 18 female (see table 5). The mean age of the participant group was 45.2 ranging from 22 to 63. Participants level of disability ranged from having no disability (EDSS =1) to being essentially wheelchair bound (EDSS=8). The mean EDSS of the study group was 4 indicating full mobility (see table 5).

7.3 Analysis

Table 5 below also provides the scores for the outcome measures used in this study namely; Fatigue severity scale (FSS), modified fatigue impact scale (MFIS), Hospital anxiety and depression scale (HAD) and Pittsburgh sleep quality index (PSQI).

Table 5: Descriptive Statistics

	N	Mean	Median	St. Dev	Range	Min	Max
Age	30	45.2	45.5	10.196	41	22	63
EDSS	30	4.0	3.50	2.304	7	1	8
FSS	30	48.83	49.00	8.267	28	33	61
MFIS	30	51.87	52.00	12.875	53	23	76
HAD	30	16.20	16.00	7.959	27	5	32
PSQI	30	8.567	7.500	4.6214	16.0	1.0	17.0

In order to carry out all the statistical analysis the study group was further divided into 2 groups (PSQI high and PSQI low); those with clinical sleep impairment (PSQI high >5) and those without clinical sleep impairment (PSQI low ≤ 5). The cut off levels used here for the PSQI scores are published and standardised (Buysse, 1989). Clinical sleep impairment scores (PSQI high >5) were found in 19 (63.3%) of the participants.

Independent- samples t-test was conducted (see table 6) to compare the EDSS, MFIS, HAD, and FSS scores for PSQI low (≤ 5) and PSQI high (>5) groups (see table6).

Table 6: T-Test Groups Low Versus High PSQI (<OR=5, OR>5)

	PSQI low	**Std.Dev low**	**PSQI high**	**Std.Dev high**	**P**
EDSS	4.91	2.386	3.47	2.144	0.101
MFIS	46.73	11.403	54.84	13.014	0.097
HAD	12.27	6.915	18.47	7.784	0.037
FSS	48.82	9.527	48.84	7.726	0.994

Accepting the statistical test for the assumption of equal variances, independent t-tests revealed that there was a significant difference in HAD scores between the 2 groups, p= 0.037 and also a trend towards significance for MFIS, p=0.097. There were no significant differences in scores for EDSS and FSS.

7.4 Hypotheses testing

These results verify and nullify the hypotheses previously stated:

- **Hypothesis Ho1** claiming no statistically significant difference between MFIS scores in a group of ms patients with (PSQI score ≤5) and without (PSQI score >5) sleep disturbance is accepted. **H1** is rejected.
- **Hypothesis H2** claiming statistically significant difference between FSS scores in a group of ms patients with (PSQI score ≤5) and without (PSQI score >5) sleep disturbance is rejected. **Ho2** is accepted.
- **Hypothesis H3** claiming statistically significant difference between EDSS scores in a group of ms patients with (PSQI score ≤5) and without (PSQI score >5) sleep disturbance is rejected. **Ho3** is accepted.
- **Hypotheses H4** claiming statistically significant difference between HAD scores in a group of ms patients with (PSQI score ≤5) and without (PSQI score >5) sleep disturbance is accepted. **Ho4** is rejected.

7.5 Post Hoc exploration

The trend towards significance for MFIS, p=0.097 (reported in 7.3) led to the MFIS scale being further divided into its sub components (MFIS cog, MFIS phys, MFIS psych), allowing further analysis of this trend.

Post-hoc exploration of the trend towards significant difference in MFIS global score (p=0.097) between high and low PSQI groups was carried out by applying separate Mann-Whitney U test analysis (non-parametric test) (see table 7) on each of the standardised and validated MFIS subscales for physical, cognitive and psychosocial aspects of fatigue. This revealed that MFIS cognitive fatigue subscale was the principal

factor explaining this trend towards significant difference (p= 0.094 compared to 0.553 and 0.216 for the other 2 subscales).

Table 7: Mann-Whitney U Test (Non-Parametric Test)

	PSQI low	**PSQI high**	**P**
MFIS phys	24.0909	25.6842	0.553
MFIS cog	18.1818	23.4211	0.094
MFIS psych	4.4545	5.7368	0.216

Further exploratory analyses were also carried out via non-parametric correlations to examine the relationship between HAD scores and MFIS scores (total score and MFIS cog). This relationship was investigated using Spearman's correlation (see figures 3&4).

Figure 3. Relationship between HAD and MFIS global scores

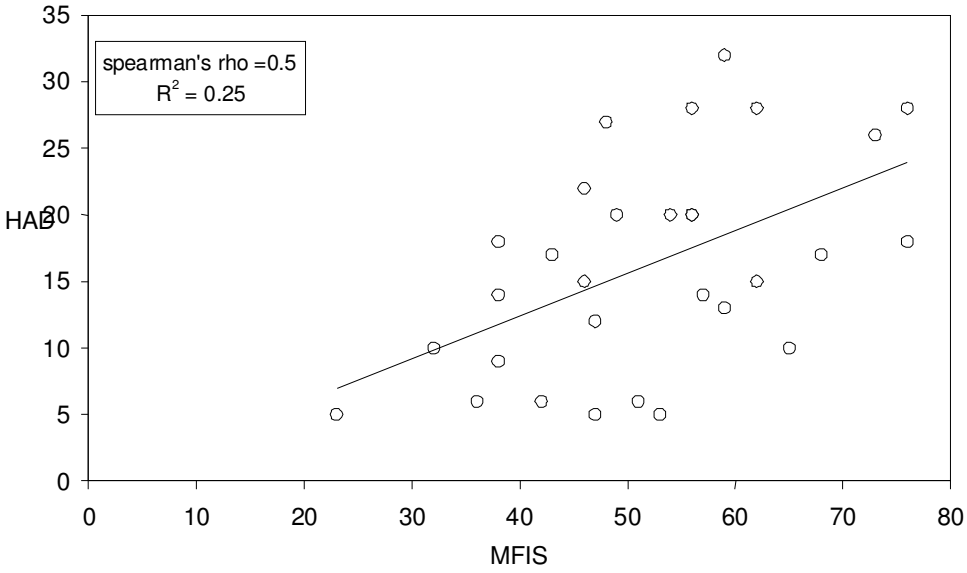
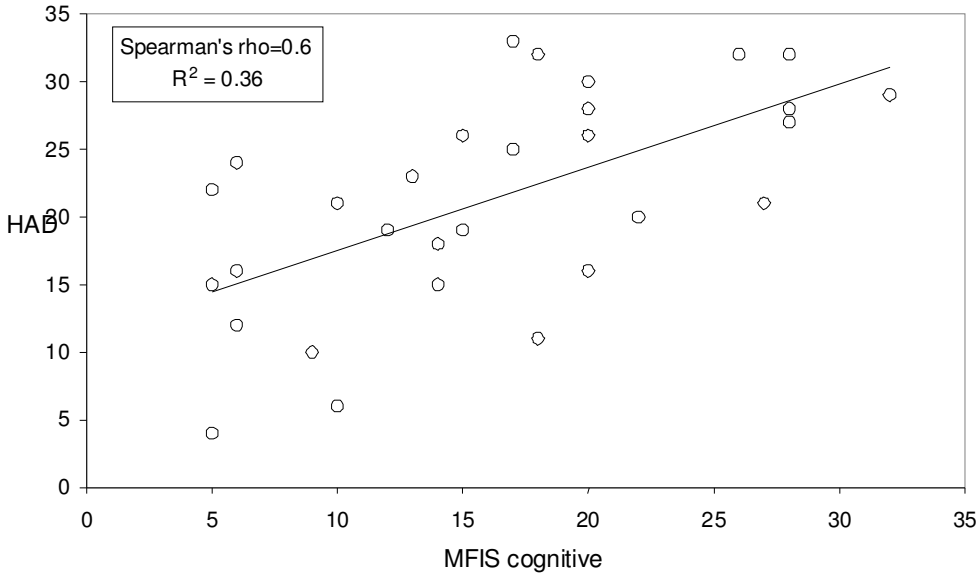


Figure 4. Relationship between HAD and MFIS Cognitive sub-scale scores



Figures 3 and 4 indicate there was a positive correlation between the 2 variables (HAD & MFIS global score) rho=0.5, R_2=0.25, n=30, p=0.005 and also HAD & MFIS Cognitive subscale score, rho=0.6, R_2= 0.36, n=30, p= 0.0

8 DISCUSSION

8.1 Introduction

A discussion now follows regarding the results of this study and how the design may have affected the outcomes. Comparison to relevant existing literature will be drawn. Recognition of limitations related to this study, subsequent clinical implications and the need for further research will also be considered.

8.2 Prevalence of sleep impairment and reported causes

In this study 63% of the study group reported sleep impairment. This concurs with a very recent paper by Merlino et al., (2009) who found half of their study participants with MS were affected by sleep impairment. Sleep disturbance in MS is therefore significantly more elevated than in the normal population which only reports 10% with sleep difficulties (Novak et al., 2008).

Further descriptive information regarding sleep impairment in the study group was provided from written responses in the PSQI scale. The responses were as Table 8:

Table 8: Causes of Sleep Disturbance

REASON FOR SLEEP DISTURBANCE	NUMBER OF PATIENTS
Up to the toilet during the night	24
Cannot breathe properly	5
Spasms	1
Cough/snoring	9
Feel too cold	10
Feel too hot	20
Bad dreams	7
Pain	20
Busy mind	2
Electric shock feeling	1

Hence the most commonly reported problems were pain, feeling too hot and getting up to the toilet at night (nocturia). They all had 20 or more out of the 30 (≥ 66.7%) participants reporting those issues to be contributing to sleep disturbance.

Getting up to the toilet and pain are common concerns within the MS population (Crayton et al., 2004). Physiological features of MS are the underlying reasons for the reported bladder difficulties and pain. These occur due to disruption of the neuronal pathways. This result is in keeping with the work of Araki et al., (2002) who reported, 70% of patients having nocturia and Osborne et al., (2008) showing 79% patients having sleep disturbance relating to pain.

However, the reported "feeling too hot" needs further clarification. This symptom has not been reported in any other literature as a reason for sleep impairment. In this study, an actual measurement of body temperature was not taken so "feeling too hot " is fairly subjective and cannot be taken to mean that the study groups body temperature actually had increased. However, it is of interest to note that many patients with MS experience a transient worsening of symptoms when body temperature increases due to ambient conditions or physical activity (Grahn, 2008). This has been thought to be due to the lack of insulating myelin sheath around the nerves in MS being exposed to heat and further impairing the conduction of the nerve (White, et al., 2000). This phenomenon of transient worsening of symptoms due to increased temperature may explain the sleep disturbance and warrants further investigation.

Patients with MS attributing specific causes for sleep disturbance should have access to individual treatment strategies (e.g. pain management, temperature control, bladder management) alongside close monitoring of the outcome in terms of sleep disturbance.

There are well recognised intervention strategies for pain management and bladder control; however, referrals to appropriate services are vital. Pain and bladder issues need to be recognised as underlying causes of sleep disturbance in order to encourage increased access to services.

In contrast, management of temperature is not well recognised or indeed treated in the current health system. White, et al., (2000) and Grahn (2008) have suggested some techniques for reducing body temperature and if future research evidences that increased body temperature affects sleep then these techniques could be considered.

White, et al., (2000) suggested that heat transfer devices incorporated into gloves or shoes could augment the use, or be used in lieu, of currently available cooling garments. Grahn et al., (2008) showed improvement in the symptoms of MS patients using their own devised cooling devise that worked on the palm of the hand.

Empowering the patient with information concerning increased body temperature and sleep impairment may allow them to implement simple strategies for keeping cool at night.

8.3 Sleep disorder and disability

This study group did not demonstrate a statistical relationship between disability (EDSS) and sleep impairment. This finding was not confirmed by Merlino et al., (2009) who found 'poor sleepers' to have significantly higher EDSS scores hence greater disability. Their sample size was bigger at 120 participants but comparable in other ways. Other studies have confirmed and found sleep disturbance to be independent of EDSS score (Stanton , Barnes & Silber, 2006; Tachibana et al., 1994).It is important to note that in current studies sleep impairment is measured using different tools and the sensitivity of these measures will affect the results that are reported. It would be extremely useful for a standard method for measuring sleep impairment to be introduced.

It could be assumed that increased disability would lead to increased sleep impairment due to restricted movement, decreased bladder control, progressive neurological symptoms and increased psychological strain. So it is of interest that this is not the finding in some of the literature. Perhaps medication or indeed an increased acceptance of the disability positively affects the ability to sleep.

In the current study the study group would have to be larger in order to confirm the direction of the correlation. The conflicting results in recent literature would benefit from further investigations into this relationship before conclusions can be made.

8.4 Sleep disorder and fatigue

Participants in this study with sleep impairment showed a trend towards more impact from fatigue (MFIS) ($p=0.097$). However the severity of the fatigue (FSS) showed no difference. The differing results from these two scales may partly be due to the way that they gather information from the subject; the MFIS examines fatigue over a month whereas FSS only reports over a week.

Literature reporting on sleep impairment and its relationship to fatigue has used different fatigue measures and as discussed earlier in relation to measuring sleep impairment, fatigue measures would benefit from being standard across research papers.

Attarian et al., (2004) showed a significant correlation between sleep impairment and fatigue. They measured fatigue using the Fatigue Descriptive Scale (FDS). In contrast, Taphoorn et al., (1993) did not show a correlation, but furthermore the studies used subjects with different levels of disability. Different measures measure different things; hence looking at fatigue in the shorter term and longer terms affects the reported results. Patients with MS have reported memory difficulties (Crayton et al., 2004) and therefore the effectiveness of collecting data that requires long term recall may be in question. The sample sizes in all studies were small (≤30).

An interesting discovery, and one that has not been highlighted in other papers, is that the cognitive subscale of the MFIS scale was the main determinant of the trend towards significance of fatigue impact with sleep impairment. This finding implies that sleep impairment may have an influence on cognition due to fatigue. In recent literature cognitive dysfunctions have been increasingly considered to be contributors to social and professional handicaps experienced by patients with MS (Schulz et al., 2006). If the relationship between these two variants works in such a way that by treating the sleep disturbance that this in return has a positive impact on patients cognitive functioning, then this would be a very exciting development for people with MS.

8.5 Sleep disorder and anxiety/ depression

The sleep impaired group (PSQI >5) were found to be more depressed/anxious than the non sleep impaired group (PSQI< 5) (p=0.037). Within this study depression and anxiety on the HAD scale were not separated which is normal practise, therefore the results reflected a combination of depression and anxiety scores. This finding concurs with Lobentanz et al., (2004) who also found that MS patients in their study with sleep impairment also had depression. In their own discussion Lobentanz et al., (2004) felt that the causal relationship was unclear; whether sleep impairment caused depression or vice versa.

As well as identifying a relationship between sleep impairment and depression this current study has also revealed relationships between anxiety/ depression and fatigue and more specifically the impact on cognitive fatigue. In this study a significant correlation was found between anxiety/depression (HAD) and Fatigue (MFIS) (Rho=0.5). Pallant, (2007) indicated that a rho value between 0.5 and 1.0 represented a strong correlation. This study has found that the more a subject was impacted by fatigue the more anxious/depressed they were. R^2=0.25 meaning the MFIS helped to explain 25% of the variance in respondents' scores on the HAD scale. This is a respectable amount of variance. Again this study cannot clearly define the causal relationships between sleep impairment, anxiety/depression and fatigue; however it could be postulated that if a patient has less sleep they experience an increased fatigue level and consequently greater anxiety/ depression. It is possible that this relationship between the variants maybe cyclic. If someone had an increase in anxiety/ depression due to other variants not measured by this study then this may consequently affect sleep or fatigue. This is obviously another area that needs further investigation in order to define the relationships further.

8.6 MFIScog subscale, sleep impairment and anxiety and depression

Previously in section 8.4 it was reported that the MFIScog subscale was the main determinant of the trend towards significance of fatigue impact with sleep impairment. This study also revealed a significant correlation between cognitive fatigue (MFIScog) and anxiety/depression (HAD). As cognitive fatigue increased in an individual so did the level of anxiety/depression; the correlation between HAD and

MFIScog was rho=0.6. , R2=0.36. This means MFIScog subscale helps to explain 36% of the variance in respondents' scores on the HAD scale. This is a respectable amount of variance. This study has identified more clearly a potential subcomponent of fatigue which seems to have a particularly strong relationship with sleep impairment and anxiety/ depression.

The result of the impact of fatigue on cognition being higher is interesting and something that has not been highlighted in other literature to my knowledge.

Feinstein (2006) carried out an extensive literature review looking at fatigue and cognition and concluded that depression may also exacerbate cognitive dysfunction in MS patients. This is mainly due to the core symptoms of depression reducing cognitive capacity, in particular exerting an adverse effect on the executive function component of working memory. Whether treating depression will lead to cognitive improvement is not yet known, but the author felt it warranted further exploration. Feinstein (2006) has further postulated that the relationship between sleep disturbance, fatigue, depression and cognition may well be cyclic, each one triggering an effect from the other e.g. as sleep impairment increases so does fatigue, depression and cognitive status and hence this cycle then triggers a further sleep impairment.

If it is found that this correlation between cognition and sleep impairment is robust then treatment options may be drawn from fields such as mental health which incorporate cognitive behavioural therapies (CBT). CBT is a group of techniques including; education on inaccurate beliefs, relaxation therapy; behaviour correction and stimulus control therapy, which is commonly used for sleep impairment in adults (Passaro 2009). CBT for sleep problems have no risk of drug related tolerance or dependency or any of the other side effects previously listed for benzodiazepines. This type of treatment aims to improve sleep by changing habits, challenging negative thoughts etc. This treatment can also have an impact on cognition, depression and its management (Montgomery & Dennis, 2009). CBT has been shown to be effective in the group situation for a range of conditions including cognitive disorders and chronic fatigue syndrome, but to date not MS. It has also been shown to be cost effective (Kipling et al., 1999; Saxty, 2005). Patients with MS find groups empowering

(Sutherland & Cowan, 2005) and such intervention would also go hand in hand in supporting the current governmental initiatives for self management (Krubb, 2003).

However, the correlation between the cognitive subscale and sleep impairment was only reported as a trend and must be interpreted with caution. Treatment options for underlying causes of sleep impairment as reported in table 5 must also be explored. CBT may well positively impact the underlying causes as reported in table 5, however, this needs to be evidenced.

9 LIMITATIONS

A limitation of this study is the sample size. The main issue that influenced the sample size of 30 was the limited time and clinics to complete the data collection and analysis for submission of this thesis.

It is important to acknowledge that the sample obtained in this study does not meet the conditions to extrapolate to the whole population (Greasley, 2008).

The lack of a control group makes it impossible to be certain that the results found were more common than those seen in the general population (Hicks, 2004).

A further limitation could be the lack of a pilot study. This was due to time limitations and the decision that the sample size may be too small to merit a pilot. A pilot study normally helps to identify such problems as; length of time it takes to complete questionnaires, problems in identifying and recruiting, time needs or confidentiality and data analysis issues to mention a few (Hicks, 2004). This may have influenced the decision for design of the study. This study itself could be viewed as a pilot with the aim to further investigate this topic which will be discussed in further research.

Qualitative investigation would allow deeper exploration into the themes around sleep disturbance and a study using both qualitative and quantitative methods may have deepened the understanding of this area (Holloway, 2002).

The study highlighted the amount of time each process takes and the researcher was limited by the time frame in which the study was to take place.

10 CONCLUSIONS

- Sleep impairment is evident in people with multiple sclerosis.
- In this small study sleep disturbance showed a trend towards significance with fatigue. The driver for this trend was the cognitive subscale for MFIS.
- There was significant difference in sleep impairment and anxiety/depression (HAD).
- There was a correlation between anxiety/depression and fatigue and again the driver for this seemed to be the cognitive subscale for fatigue.
- There was no significant difference between sleep impairment and disability.

Sleep disturbance is beginning to be accepted as a common concern for people with ms, the consequences and underlying reasons of which are beginning to be explored in literature. Access and ongoing research into effective treatment for sleep disturbance in MS is in its infancy, and requires further exploration in order to manage this particular deficit effectively.

This study has highlighted a relationship between cognitive fatigue and sleep impairment and cognitive fatigue and anxiety/ depression. If these results were replicated within a bigger cohort then it would have significant implications for the type of treatments trialled for this particular problem.

Boggild (2005) identified that all professionals dealing with people with MS should increase their competencies in identifying and intervening for sleep disturbances. Furthermore, if the results of this study are seen to be robust then Boggild's conclusions further by suggesting that professionals not routinely involved in the care of this patient group may be appropriate for treating their sleep disturbance. Professionals who have competencies in cognitive behavioural therapies (CBT) may offer the MS population a treatment which most meets their needs in terms of resolving/improving their sleep disturbance. This would offer exciting new avenues of intervention and research in the emerging area of sleep disturbance in MS.

Symptomatic treatment of MS should be comprehensive and integrated in nature and needs to begin to incorporate measures for identifying and treating sleep impairment. Stanton, Barnes & Silber (2006) observed that sleep services in the UK were overrun, preventing every client with MS from accessing this specialist service. As a solution, Stanton, Barnes & Silber (2006) suggest that all professionals dealing with people with MS should develop their understanding of sleep disturbance in order to facilitate appropriate intervention.

Sleep disturbance may be due to a variety of symptoms related to MS and many of those symptoms are treatable. It would be recommended that questions about sleep are included in the routine assessment by health professionals.

KEY CLINICAL MESSAGES:

- Health professionals need to become aware of sleep disturbance in the MS population.
- Investigation of sleep disturbance should be an integral part of the routine neurological assessment.
- Health professionals dealing with MS need to develop their understanding of sleep disturbance.
- Care pathways need to be identified for the treatment of sleep disturbance.
- Future direction for effective and efficient intervention for sleep disturbance should come from such directives as SIGN or NICE guidelines.

This study although small in sample size has added to current literature in highlighting the problem of sleep disturbance in multiple sclerosis and its associations with other variables. However further research with larger cohorts is needed to confirm the trends that have been evidenced in this study.

11 FUTURE RESEARCH

1. The causes and implications of sleep disturbance could be investigated further with a larger sample size and also with additional qualitative data.
2. Does the body temperature of MS patients rise during sleep and if so what are the underlying causes?
3. Is the use of CBT effective in treating sleep impairment in people with MS? And if so does it also positively impact cognition.
4. A study using a larger cohort is required to examine the relationship between MFIScog and sleep impairment.
5. Further investigation into levels of disability and sleep impairment as this relationship still remains unclear in terms of investigative research.

12 APPENDIX 1 – INFORMATION SHEET

INFORMATION SHEET

An investigation into sleep disturbance in multiple sclerosis

Invitation to participate

We would like to invite you to participate in a new research study. Before you decide whether or not to participate, it is important for you to understand why the research is being done and what it will involve. This information sheet explains the background and aims of the study. Please take time to read it carefully and discuss it with family and friends or your own doctor or physiotherapist if you wish. If there is anything that is unclear, or if you would like more information, please ask us. Your participation in this study is entirely voluntary.

Why have I been chosen?

You have been chosen because you have a diagnosis of MS and attend the MS specialist clinic at the Western general hospital.

In total 30 people with MS from this clinic will be participating in this research study.

What is the overall aim of the study?

Sleep disturbance in multiple sclerosis (MS) appears to be common, although clinically under recognised. Literature describing fatigue in MS also highlights that sleep disturbance is an area that has little investigation, yet could be an important secondary cause of fatigue. To date there has been no clear research which examines the possible causes of sleep disturbance with a view to intervention.

The aim of this study is to investigate sleep disturbance in multiple sclerosis and its relationship to fatigue with a view to potentially improving future treatment of this symptom.

What would I have to do if I took part in this study?

You will be asked to read an information sheet and if willing then sign a consent form. Your participation will be required for about an hour if you agree to take part in this study and will involve filling in four questionnaires. The questionnaires are; Fatigue severity, Modified fatigue impact, Pittsburgh sleep quality index and Hospital anxiety and depression. The majority of which are tick box answers. This will be done sitting in the MS specialist clinic at the Western General hospital. This will involve one extra visit to the MS specialist clinic at the Western General hospital only.

Do I have to take part?

No. Participation in this study is entirely voluntary and if you decide not to take part your usual medical care will not be affected in any way.

Will the study involve taking any new medication?

No. We will not change your existing medication or prescribe any new interventions during the period that you are involved in this study.

Will I have to make any extra visits to my neurologist or GP?

You will not have to make any extra visits to your GP or to your neurologist.

What happens when the research study stops?

At the end of the study you will continue to receive the usual treatment that the physiotherapist provides.

Will my records be confidential?

All information collected about you during the project will be kept strictly confidential. You will be allocated a project number which we will use on all assessment records rather than your full name or other identifying details. Your name and address will be stored separately from the other information you supply during the project so that you cannot be identified from your study records. If you choose to discontinue being

involved in the study your data will be destroyed. All information will be handled in compliance with the Data Protection Act (1998).

What are the potential benefits of taking part in this study?

You should understand that you may not gain benefits from filling in the questionnaires. However the results of the study may highlight areas that potentially in the future may improve quality of life for people with multiple sclerosis.

What are the potential risks of taking part in this study?

The only risk highlighted is that it may be tiring to fill in the questionnaires and for that reason you can take as long as you require to fill them in. Taking breaks as necessary.

Who is organising the study?

The project is being organised by Paula Cowan (MS Specialist Physiotherapist) who is in her final year of MSc in Multiple sclerosis at Leeds Metropolitan University. This is part of her final dissertation.

Who has reviewed this study?

This study has been reviewed and approved by; NHS Lothian University Hospital Division (DH 2004, 2005) and the Lothian Research & Ethics Committee (DH 2005); Leeds Metropolitan University policy and procedure for research ethics.

What if something goes wrong?

If you wish to complain, or have any concerns about this study then in the first instance please contact the researcher whose details are at the end of the Information Sheet.

The Patient Liaison Service for Western General Hospital is also there to help, and is available via telephone 0131 242 3379. The normal National Health Service complaints mechanisms should also be available to you.

How will I hear about the results of the study?

We anticipate that it will take approximately 9 months to be completed. At the end of this period, if you wish, we will send you a summary of the results of this study.

Your rights

Your participation in this study is entirely voluntary. You may withdraw at any time without it affecting your current or future medical treatment in any way. If you agree to take part in this study, you will need to sign a consent form.

Contact for further information

If you require any further information about this study, or have any questions please contact Paula Cowan on 0131 537 2113 during office hours.

Other research members contacts: Dr Belinda Weller (Consultant Neurologist) 0131 537 1441, Liz Mackay (Chief Investigator/ Tutor at Leeds Metropolitan University) 01138125820.

Thank you for reading this Information Sheet and considering taking part in the study. If you decide to participate in this study you will be given a copy of this Information Sheet and a signed consent form to keep.

13 APPENDIX 2 – CONSENT FORM

CONSENT FORM

Title of Project: An investigation into sleep disturbance in multiple sclerosis

Name of Researcher: Paula Cowan

Please note that if you have any unanswered questions about this study then you should NOT complete this form.

CONSENT FORM

Title of Project: An investigation into sleep disturbance in multiple sclerosis

PLEASE INITIAL ALL BOXES

1	I confirm that I have read and understood the information sheet (version 2 23/03/09) for the above study and have had the opportunity to ask questions.	
2	I confirm that I have had the opportunity to discuss the study with the researcher. I do not have any further questions about this study.	
3	I understand that the information collected during this study will remain strictly confidential and accessible only to appropriate members of the research team.	
4	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical or physiotherapy care or legal rights being affected.	
5	I understand that I can obtain a copy of the results following the analysis of the study.	
6	I agree to my GP being notified of my participation if necessary	
7	I agree to take part in the above study	

Name of Patient

Date **Signature**

Name of Person Taking Consent

Date **Signature**

Copy for patient; Copy for researcher; Copy to be kept with patient notes

14 APPENDIX 3 – GP LETTER

GP LETTER

Date:

Dear

Re: An investigation into sleep disturbance in multiple sclerosis

I am writing to inform you that *(name of patient)* who is registered as a patient in your Practice has consented to participate in this study. This study is being carried out by myself at the western general hospital and will be supported by the MS specialist neurologist.

I am using a single cross sectional cohort study involving the use of 4 questionnaires namely; fatigue severity scale, Modified fatigue impact scale, hospital anxiety and depression scale and the Pittsburgh Sleep quality index.

A standardised protocol for the study is being used throughout the research process and ethical approval has been obtained.

The study will take place at the MS clinics in the western general hospital on a Monday or Wednesday morning. Participants may of course withdraw from the study at any time without penalty.

The following patient has consented to take part in this study.

Patient name: _____

Patient address: _____

Patient DOB: _____

Patient Hospital Number: _____

If you require any further information, please contact me on 0131 537 2113

Yours sincerely

Paula Cowan

MS Specialist Physiotherapist and Researcher for this study

15 APPENDIX 4 – DEMOGRAPHIC DATA

DEMOGRAPHIC DATA

PATIENT ID CODE:	
SEX:	
AGE:	
DATE OF DIAGNOSIS:	
TYPE OF MS:	RR / SECONDARY PROGRESSIVE / PRIMARY PROGRESSIVE
EDSS SCORE:	

CO-MORBIDITY:

CURRENT MEDICATION:

COMMENTS:

16 APPENDIX 5 – PITTSBURGH SLEEP QUALITY INDEX

ID Code:	Date:

PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

   BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

   GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

   HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Wake up in the middle of the night or early morning

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Have to get up to use the bathroom

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

d) Cannot breathe comfortably

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Cough or snore loudly

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

f) Feel too cold

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

g) Feel too hot

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

h) Had bad dreams

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

i) Have pain

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

j) Other reason(s), please describe_____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?

Very good _____

Fairly good _____

Fairly bad _____

Very bad _____

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

Somewhat of a problem _____

A very big problem _____

10. Do you have a bed partner or room mate?

No bed partner or room mate _____

Partner/room mate in other room _____

Partner in same room, but not same bed _____

Partner in same bed _____

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

a) Loud snoring

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Long pauses between breaths while asleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Legs twitching or jerking while you sleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

d) Episodes of disorientation or confusion during sleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Other restlessness while you sleep; please describe_____

_____

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

17 APPENDIX 6 – FATIGUE SEVERITY SCALE

ID Code:	Date:

FATIGUE SEVERITY SCALE QUESTONNAIRE

The fatigue Severity Scale (FSS) is a method of evaluating the impact of fatigue on you. The FSS is a short questionnaire that requires you to rate your level of fatigue.

The FSS questionnaire contains nine statements that rate the severity of your fatigue symptoms. Read each statement and circle a number from 1-7, based on how accurately it reflects your condition during the past week and the extent to which you agree or disagree that the statement applies to you.

A low value (e.g. 1) indicates strong disagreement with the statement, whereas a high value (e.g. 7) indicates strong agreement.

It is important that you circle a number 1-7 for every question.

During the past week I have found that:	**Disagree ←----------→ Agree**						
My motivation is lower when I am fatigued	1	2	3	4	5	6	7
Exercise brings of my fatigue	1	2	3	4	5	6	7
I am easily fatigued	1	2	3	4	5	6	7
Fatigue interferes with my physical functioning	1	2	3	4	5	6	7
Fatigue causes frequent problems for me	1	2	3	4	5	6	7
My fatigue prevents sustained physical functioning	1	2	3	4	5	6	7
Fatigue interferes with carrying out certain duties and responsibilities	1	2	3	4	5	6	7
Fatigue is among my three most disabling symptoms	1	2	3	4	5	6	7
Fatigue interferes with my work, family or social life	1	2	3	4	5	6	7
	Total Score:						

18 APPENDIX 7 – MODIFIED FATIGUE IMPACT SCALE

ID Code:	Date:

MODIFIED FATIGUE IMPACT SCALE (MFIS)

Following is a list of statements that describe how fatigue may affect a person. Please read each statement carefully and then circle the ONE number that best indicates how often fatigue has affected you in this way during the past 4 weeks. Please answer every question.

Because of my fatigue during the past 4 weeks:	**Never**	**Rarely**	**Sometimes**	**Often**	**Almost Always**
1. I have been less alert	0	1	2	3	4
2. I have had difficulty paying attention for long periods of time	0	1	2	3	4
3. I have been unable to think clearly	0	1	2	3	4
4. I have been clumsy and uncoordinated	0	1	2	3	4
5. I have been forgetful	0	1	2	3	4
6. I have had to pace myself in my physical activities	0	1	2	3	4
7. I have been less motivated to do anything that requires physical effort	0	1	2	3	4
8. I have been less motivated to participate in social activities	0	1	2	3	4

Because of my fatigue during the past 4 weeks:	**Never**	**Rarely**	**Sometimes**	**Often**	**Almost Always**
9. I have been limited in my ability to do things away from home	0	1	2	3	4
10. I have had trouble maintaining physical effort for long periods	0	1	2	3	4
11. I have had difficulty making decisions	0	1	2	3	4
12. I have been less motivated to do anything that requires thinking	0	1	2	3	4
13. My muscles have felt weak	0	1	2	3	4
14. I have been physically uncomfortable	0	1	2	3	4
15. I have had trouble finishing tasks that require thinking	0	1	2	3	4
16. I have had difficulty organising my thoughts when doing things at home or at work	0	1	2	3	4
17. I have been less able to complete tasks that require physical effort	0	1	2	3	4
18. My thinking has been slowed down	0	1	2	3	4
19. I have had trouble concentrating	0	1	2	3	4
20. I have limited my physical activities	0	1	2	3	4
21. I have needed to rest more often or for longer periods	0	1	2	3	4

19 APPENDIX 8 – HOSPITAL ANXIETY & DEPRESSION SCALE

ID Code:	Date:

HOSPITAL ANXIETY AND DEPRESSION SCALE (HAD)

Please tick a box for each question that best describes how you feel.

	Yes Definitely	Yes Sometimes	No, Not Much	No, Not at all
1. I wake early and then sleep badly for the rest of the night				
2. I get very frightened or have panic feelings for apparently no reason at all				
3. I feel miserable and sad				
4. I feel anxious when I go out of the house on my own				
5. I have lost interest in things				
6. I get palpitations, or sensations of 'butterflies' in my stomach or chest				
7. I have a good appetite				
8. I feel scared or frightened				
9. I feel life is not worth living				
10. I still enjoy the things I used to				
11. I am restless and can't keep still				
12. I am more irritable than usual				

	Yes Definitely	Yes Sometimes	No, Not Much	No, Not at all
13. I feel as if I have slowed down				
14. Worrying thoughts constantly go through my mind				

20 APPENDIX 9 – ETHICAL APPROVAL LETTER

Lothian NHS Board

Lothian Research Ethics Committee 02
Deaconess House
148 Pleasance
Edinburgh
EH8 9RS
Telephone 0131 536 9000
Fax 0131 536
www.nhslothian.scot.nhs.uk

NHS Lothian

Ms Paula Cowan
DCN Physiotherapy Dept
Western general Hospital
Crewe Road South, Edinburgh
EH4 2XU

Date 15 April 2009
Our Ref
Enquiries to Lyndsay Baird
Extension 89061
Direct Line 0131 536 9061
Email lyndsay.baird@nhslothian.scot.nhs.uk

Dear Ms Cowan

Full title of study: **An Investigation into Sleep Disturbance in Multiple Sclerosis**

REC reference number: **09/S1102/9**

Thank you for your letter of 23 March 2009, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered at the meeting of the Committee held on 15 April 2009.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

To note: the committee had requested that the title of the research is on the signature page. Please amend the consent form accordingly and send a copy to our office for the file.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

21 APPENDIX 10 – MANAGEMENT APPROVAL LETTER

University Hospitals Division
Queen's Medical Research Institute
47 Little France Crescent, Edinburgh, EH16 4TJ

NHS Lothian

DEN/JB/approval/2e

13 March 2009

RESEARCH & DEVELOPMENT
Room E1.12
Tel: 0131 242 3330
Fax: 0131 242 3343
Email:
R&DOffice@luht.scot.nhs.uk

Director:
Professor David E Newby

Ms Paula Cowan
Specialist Physiotherapist
Western General Hospital
Crewe Road
Edinburgh
EH4 2XU

Dear Ms Cowan

MREC No:	**09/S1102/09**
CRF No:	**N/A**
LREC No:	**09/S11ADMIN/19**
R&D ID No:	**2009/W/PSY/03**
Title of Research:	*An investigation into sleep disturbance in Multiple Sclerosis*
Protocol No/Acronym:	**Version 1 dated 03 February 2009**

The above project has undergone an assessment of risk to NHS Lothian and review of resource and financial implications. I am satisfied that all the necessary arrangements have been set in place and that all Departments contributing to the project have been informed.

I note that this is a multi centre study sponsored by **Leeds Metropolitan University.**

On behalf of the Chief Executive and Medical Director, I am happy to grant management approval from NHS Lothian to allow the project to commence, subject to the approval of the appropriate Research Ethics Committee(s) having also been obtained. You should note that any substantial amendments must be notified to the relevant Research Ethics Committee and to R&D Management with approval being granted from both before the amendments are made.

This letter of approval is your assurance that NHS Lothian is satisfied with this project. For approved research, NHS Lothian will provide cover for negligence for NHS and Honorary clinical staff for research associated with their clinical duties. It is not empowered to provide non-negligent indemnity cover for patients.

As Chief Investigator or local Principal Investigator, you should be fully committed to your responsibilities within the Research Governance Framework for Health and Community Care, an extract of which is attached to this letter.

Yours sincerely

Professor David E Newby
R&D Director

enc
- Research Governance Certificate ☑ (to be signed and returned)
- Tissue Policy (if applicable) ☐
- MTA (if applicable) ☐ (to be signed and returned)

cc *Administrators, Research Ethics Committee*
Ms Liz Mackay, Facility of ealth, Civic Quarter, Leeds Metropoliton University, Leeds, England, LS1 3HE

"Improving health through excellence and innovation in clinical research"

Lothian Local Research Ethics Committee 02

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	09/S1102/9	**Issue number:**	1	**Date of issue:**	15 April 2009
Chief Investigator:	Mrs Liz Mackay				
Full title of study:	An Investigation into Sleep Disturbance in Multiple Sclerosis				

This study was given a favourable ethical opinion by Lothian Local Research Ethics Committee 02 on 15 April 2009. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	*Post*	*Research site*	*Site assessor*	*Date of favourable opinion for this site*	*Notes (1)*
Mrs Paula Cowan	MS Specialist Physiotherapist	NHS Lothian	Lothian Admin	15/04/2009	

Approved by the Chair on behalf of the REC:

..... (Signature of ~~Chair~~/Co-ordinator)

(delete as applicable)

L BAIRD. ..... (Name)

(1) *The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension of termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.*

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