Exploring the Beliefs and Underlying Functional Deficits
Associated with Chronic Fatigue Syndrome and the
Identification of Predictors of Recovery and Successful
Illness Management

A Submission for the Award of PhD by Published Works
to
University of Wales Institute Cardiff

Marie Thomas
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FOREWORD

Chronic Fatigue Syndrome is described as an illness that produces a marked reduction in activity and an increase in mental fatigue. The condition, as the name suggests, is chronic in nature and is of sufficient severity to cause substantial functional impairment to the sufferer and exerts a significant financial drain on healthcare and welfare resources. It was the culmination of these factors which prompted the call for structured and wide-ranging programmes of research in the United Kingdom. The research project described in the following chapters was conducted in response to this call. The preliminary narrative begins with a brief introduction to the project's scope, a description of the clinical setting for the project and the participants taking part and will end with an account of my involvement in the research.

I The Cardiff Chronic Fatigue Syndrome (CFS) Research Project

The submitted work draws on findings from two successive research projects into Chronic Fatigue Syndrome (CFS) conducted as part of the Cardiff CFS Research Project:

1. ‘The role of psychosocial factors and recurrent infection in the pathogenesis of the Chronic Fatigue Syndrome’ funded by the Linbury Trust

2. ‘Healthcare evaluation and assessment of patient education in Chronic Fatigue Syndrome’ funded by the Gatsby Foundation.

The research was conceived as a direct result of a report from a consensus meeting in 1990 (Sharpe, et al., 1991). This meeting of a multi-disciplinary group of eminent

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1 The Linbury Trust and the Gatsby Foundation form part of the Sainsbury family’s group of charitable trusts which has been an important patron in CFS research.
scientists at Green College, Oxford aimed to provide more structure for the definition of this illness (and nomenclature used), the type of person affected, the symptoms it presents and the direction of future research (Sharpe et al., 1991). The meeting produced a set of guidelines which would shape the nature and direction of future studies and concluded that: 'The contributors hope that these guidelines will provide a basis for fruitful research studies and for inter-disciplinary collaboration essential to this field of research. The guidelines are preliminary and will undoubtedly require further refinement and revision’ (p. 121).

This pivotal report will be discussed in greater detail in the critical analysis as it identifies the gaps within the scientific knowledge that existed at the time and, therefore, shaped not only the nature of the Cardiff project, but the majority of the CFS studies conducted in the UK. Moreover, the report was instrumental in the inception of a specialist out-patient clinic at the University Hospital of Wales.

II The CFS Out-patient Clinic

The CFS out-patient clinic was established in 1991 by Professor Sir Borysiewicz and supervised by the Department of Medicine’s Section of Infectious Diseases. Primarily designed as a research vehicle and initially funded by the Linbury Trust, the clinic accepted patients from the primary healthcare setting by standard National Health Service (NHS) referral. Each referred patient was assessed by a research registrar who completed a full clinical history and examination on a standardised pro forma. The major features of the disease, such as the nature and duration of fatigue and precipitating factors of disease exacerbation, were recorded. Standard clinical and biochemical investigations (including erect and supine blood pressure, echo cardiogram and physical examination, full blood work, viral screen and immune status) were performed in order
to determine possible mechanisms for the illness and to rule out other diseases presenting with clinical fatigue.

The remit of the clinic also encompassed investigations into the nature and extent of behavioural and immunological abnormalities associated with the syndrome and the roles of: psychosocial factors in modifying the features and persistence of the illness; recurrent infections in the persistence of the disease; and the above factors in influencing the efficacy of both conventional and alternative therapies.

Initial studies into the psychological nature of this disorder were conducted at the Health Psychology Research Unit at the University of Wales College Cardiff and the Health Psychology Research Unit at the University of Bristol. The latter stages of the project were conducted at the Centre for Occupational and Health Psychology at Cardiff University. Each stage of the research was supervised by the Director of the research unit Professor Smith who was Principal Investigator along with Professor Sir Borysiewicz.

Unfortunately, closure of the outpatient clinic in 2001 resulted in a shift of responsibility for CFS management back to primary care where, as sufferers are well aware, treatment becomes somewhat of a lottery. Methods for diagnosing and managing CFS remain controversial as is indeed the very existence of the illness. The problems associated with these issues are discussed in the main body of work along with factors surrounding recovery from the untreated illness.

The research projects described in the submitted Thesis has offered me an opportunity to investigate a controversial and often misunderstood illness. As indicated in the chapters that follow, although relatively rare, Chronic Fatigue Syndrome presents myriad symptoms of varying severity which causes extreme distress, not only to the individual
sufferer, but to the friends and family of those it affects. In spite of this, the participants involved in the studies offered their unwavering support to this long-term undertaking.

The Thesis will begin by stating the University of Wales' requirements for the award of PhD by Published Works and will go on to provide a brief overview of the submission. This will be followed by a critical analysis which aims to place the body of work into a scientific context and identify its contribution to the existing knowledge base. The Thesis will end by examining possible directions for future research in light of the findings detailed in the body of work.

II Acknowledgements

To Dr Llewelyn and Mr Sadlier for allowing me the opportunity to attend consultations and for imparting their substantial knowledge and insight into the illness that is CFS. Most importantly, to all the people who took part in the research.
CRITICAL ANALYSIS

The research discussed in the Thesis contributes to the development of valid management guidelines for Chronic Fatigue Syndrome (CFS) based on the principles of evidence-based research. This wide-ranging project describes developments in the following areas:

1. The study of the disease, its impact on and the substantial problem it causes for primary and secondary care, patients, families and society by evaluating patient perceptions, beliefs and responses to healthcare in South Wales;

2. The documentation of the current position, development of case definitions and conducting biopsychosocial research on assessment and pathogenesis of the disease;

3. The identification of patient characteristics associated with successful treatment outcomes;

4. The development of a strategy for evaluating healthcare provision for CFS;

5. The evaluation of healthcare services for patients with CFS both in Wales and across the United Kingdom.

This research was not investigating the aetiology of the illness as analyses were conducted retrospectively. Rather the aims of the project were to delineate subgroups within CFS and to examine whether specific outcome measures act as good objective markers of clinical improvement and, more importantly, to explore therapeutic options available to such patients.
1. An Evaluation of the Field of Study

In order to understand the controversy surrounding this illness it is necessary first to consider the historical context. The history of the illness currently referred to as Chronic Fatigue Syndrome (CFS) stretches back over many years. The illness has been re-defined over time and this is reflected in the changes in nomenclature used to describe it and the way in which the scientific community has chosen to research it. Wessely presented an historical background of the illness in a supplement dedicated to Post Viral Fatigue Syndrome (the name used for chronic fatigue at that time) in the British Medical Bulletin in 1991 (Wessely, 1991). His in-depth essay charted, not only the emergence of the illness in the medical literature, but went some way to explain the cultural attitudes towards this type of condition in society. It will be used here to draw attention to the magnitude of the problem unexplained fatigue has posed to the medical profession itself, and to sufferers and carers also.

The evaluation of the literature will then discuss the ways in which experts in the field have tried to unravel the complex mechanisms which may be responsible for causing the illness and/or maintaining it as well as investigating factors associated with it. Following on from this, the development of management and treatment strategies will be discussed. To place these subjects within the context of the papers being presented in the proposed Thesis, three major mile-stone publications responsible for driving this research forward in the UK will be reviewed.

1.1 The Emergence of Chronic Unexplained Fatigue in the Medical Literature

The disease first came to prominence in the medical literature in the mid-nineteenth century (circa 1860-1880) and was described as a weakness of the nervous system – neurasthenia. Neurasthenia, as the name suggests, was originally grounded within the
emerging discipline of Neurology. Initially, experts in the field believed that the disease affected only the most intellectual and hard-working members of the higher social classes and was viewed as a consequence of raised expectations brought about by the rise of Capitalism. It was later described as exhaustion of the central nervous system attributed to the failure of cerebral blood flow, a deficiency in energy sources, a genetic fault or the excessive demands made on the body by toxic, metabolic or infective agents (Cobb, 1920; Foster, 1900; Pershing, 1904). In 1920, Cobb went on to state that Neurasthenia was: 'a condition of nervous exhaustion, characterised by undue fatigue on slightest exertion, both physical and mental, with which are associated symptoms of abnormal functioning, mainly referable to disorders of the vegetative nervous system' (p. 920). As a consequence, treatments centred on those aiming to stimulate the fatigued system or to sedate over-activity, to replace lost energy by the application of electrical stimulus or to recuperate lost energy (the rest cure).

The diagnosis of neurasthenia declined shortly afterwards when dissenters began to question the organic basis of the disease. It became viewed as a diagnosis made: 'for the comfort of the relatives and peace of mind of the patient' (Risien, 1913, p. 925) as it avoided the stigma of psychiatric illness and treatment in an asylum. Such comments were responsible for the gradual shift in the search for an aetiological explanation from within the discipline of Neurology to that of Psychiatry. This was accompanied by modifications to the definition of the illness to one of a mild melancholic, anxious or depressive state together with a concomitant change in possible treatments offered. The first Occupational Therapy programmes were being developed at that time and activity (or exercise) with complementary psychotherapy began to replace the rest cure and sanatoria (Hall, 1905). Due to the lack of a cellular basis for the fatigue, rest was believed to be unnecessary and ill-advised. Symptoms of the illness were now more likely to be
described as psychological. Terms such as ‘painful fatigue’ were replaced by terms such as ‘anhedonia’ (Myerson, 1922). Moreover, Tinel (1941) stated that ‘all neurasthenic states are in reality depression – perhaps minor, attenuated, atypical, masked, but always forms of anxious melancholia’ (p. 926).

Despite the change in the way the illness was being viewed, some researchers continued to search for an organic basis to the illness. Early research had already referred to neurasthenia as the toxic state and a link with infective agents was thus made (Van Deusen, 1869 for example). The observation that the illness often followed an infection (most noticeably influenza) led to the emergence of the term Post Viral Fatigue Syndrome (PVFS). However, it quickly became clear that this neurasthenic condition could follow any viral infection, especially where co-morbid anxiety or depression were manifest (Ash, 1909; Lane, 1906). Nevertheless, this did not dissuade continued research into possible causes due to infection. As recently as 1985, researchers reported findings suggesting that the Epstein-Barr virus (EBV) was the causative agent leading to the introduction of the label ‘chronic Epstein Barr infection’ to the growing list of names for this baffling disease (Straus, et al., 1985).

Another diagnosis of chronic fatigue which has generated great interest within the scientific community and society is Myalgic Encephalomyelitis (ME). This term was first used in 1955 following a mysterious outbreak of a fatiguing illness which afflicted the majority of staff at the Royal Free Hospital in London (as documented by Ramsay in 1986). This so called benign myalgic encephalomyelitis was thought to be infectious in nature (Medical Staff of the Royal Free Hospital, 1976). These claims could not, however, be substantiated and were famously contradicted by McEvedy and Beard who, whilst agreeing that the outbreak was contagious, considered that the contagion was one
of mass hysteria (McEvedy & Beard, 1970). As both represent uncorroborated viewpoints the matter remains unresolved but contentious.

The incidence of ME as an epidemic waned over time with sporadic cases coming to the fore (Smith, 1989). During the 1980s, these intermittent cases became more widespread and the outlook for the individual sufferer became bleak. In a repeat of the route taken by neurasthenia, the fatigue experienced in ME was at first thought to be neuromuscular in origin and treatments once again centred on the rest cure. However, although the theories put forward were supported by data from electromyography (EMG) and nuclear magnetic resonance (NMR) studies, doubt remained as to their validity (see Jamal & Millar, 1991 for a review). It was then believed that the illness was caused by changes to the central nervous system (CNS) and, in almost a repeat of what occurred previously in the history of unexplained fatigue, the aetiological route of ME finally arrived at the psychological. ME remains the name of choice for the majority of support groups with some offering tacit acknowledgement of its current nomenclature by referring to the illness as CFS/ME.

The term Chronic Fatigue Syndrome first appeared in the medical literature in 1988 in both the USA (although the term chronic fatigue and immune deficiency syndrome (CFIDS) was more likely to be used by patient groups) and Australia (Homes, et al., 1988; Lloyd et al., 1988). Unlike neurasthenia and ME, initial research into the aetiology of CFS centred on the role of viruses, namely the Epstein-Barr virus (responsible for causing infectious mononucleosis) in the USA and enteroviruses (originally the polio virus) in the UK.

The substantial body of research investigating the aetiology of CFS and the identification of biological diagnostic markers conducted over many years has been to no avail. Indeed, early reports of an association between the illness and a number of possible
causative infective agents have unfortunately not been substantiated (Dismukes, et al., 1990; Straus, et al., 1988). That said, persistent viral infection had been suggested as a possible mechanism for perpetuation of the illness (Archard, et al., 1988; Bowles, 1993; Cunningham, et al., 1990). Furthermore, studies indicating increased susceptibility to infections in patients suffering psychological stress may also explain the circumstances seen in CFS (Cohen, et al., 1993; Cohen, et al., 1991; Cohen & Williams, 1991). In fact, a major impact of the disease on the patient has been described as one of a ‘chronic, recurring, flu-like illness’ (Dubois, et al., 1984; Jones et al., 1985; Komaroff, 1991; Straus, et al., 1985). Anecdotally, CFS patients frequently report symptoms of recurrent infections and these infections have been implicated as a possible means whereby the illness is exacerbated (Smith, 1991) although such claims have not been tested under controlled experimental conditions.

The lack of evidence (once again) pointing to an organic basis for the illness did not, however, result in a decline in scientific interest. The incidence of CFS was rising in the UK and primary and secondary healthcare providers were coming under increasing pressure to offer a service to these sufferers. But for the NHS to provide a service for patients, further research was needed to understand the factors associated with the illness and also factors identified as being responsible for perpetuating it together with an appropriate clinical management strategy. The narrative that follows discusses the three publications judged most influential in shaping the nature and direction of the Cardiff CFS Project and provide the framework within which the body of research is evaluated. The first, the 1991 Guidelines for Research (Sharpe, et al., 1991), aims to set out a detailed description of the illness in order to facilitate the investigation of possible mechanisms causing and/or perpetuating it.

1.2 Milestones in the Literature Shaping the Direction of Chronic Fatigue Syndrome Research
i) Guidelines for Research

In 1990 a meeting, in Oxford, of leading experts within the field of CFS study (including Professors Smith and Borysiewicz) produced a draft consensus document recommending guidelines for future research into the syndrome (Sharpe, et al., 1991). The purpose of the meeting was to provide a platform in order to bring clarity to the contradictory findings from previous multi-disciplinary research: 'The aim of the meeting was to seek agreement amongst research workers on recommendations for the conduct and reporting of future studies of patients with chronic fatigue. Specifically we set out to agree on which patients should be included, how such studies should be approached and on the minimal data that should be reported' (p. 119). In a paper documenting the meeting, it was acknowledged that although an increasing amount of research was being conducted into CFS, the diversity of the disciplines involved, together with the differing criteria being used to define the illness, meant that studies were not always comparable: 'Agreement on case definition and assessment methods is necessary if progress is to be made' (p. 118).

In an introduction to the Guidelines, the report discussed issues surrounding the definition of the illness and, in particular, the lack of agreement when describing the groups of patients being studied. This discord, as suggested previously, was primarily due to the range of illnesses included within this syndrome such as benign Myalgic Encephalomyelitis, chronic infectious mononucleosis, Post Viral Fatigue Syndrome, Royal Free disease and Chronic Fatigue Syndrome. Although patients suffering from these conditions present with similar symptom patterns, the description of each syndrome differed sufficiently to make meaningful comparison between studies unfruitful. Moreover, among other things the description of sampling methods, the use
of comparison groups, inadequate study design and unreliable assessment measures were cited as probable barriers to conceptual agreement in CFS research (Sharpe et al., 1991).

The report aimed to address these issues in the first instance by setting out a preliminary research glossary providing provisional definitions of the major symptoms experienced, namely fatigue, disability, mood disturbance, myalgia (muscle pain) and sleep disturbance. It was then recommended that each of these five symptoms should be considered separately. There was the need for accurate, detailed descriptions of each symptom. The fatigue experienced in CFS can be both mental and physical (for example, mental fatigue can be characterised by low alertness and physical fatigue as a lack of energy or strength in the muscles). Following on from this was the need to delineate the way in which each symptom should be distinguished from others (for example, the symptom of fatigue being distinguished from one of low mood). Addressed next were the criteria for rating each symptom’s presence (for example, the fatigue experienced should have significant effect on a person’s functioning). Finally, it was acknowledged that it may be necessary to describe each symptom in additional detail (for example, the fatigue experienced could be described as mild, moderate or severe).

The report went on to acknowledge that there were no clinical signs that could be used to characterise the illness. It was recommended, however, that the absence or presence of signs should be documented. It was further proposed that the condition should be defined as one of two syndromes: either Chronic Fatigue Syndrome or Post-infectious Fatigue Syndrome (PIFS). PIFS was defined as a sub-type of CFS which followed or was associated with an infective episode. The definition of CFS proposed and agreed at the meeting formed the basis of the Oxford criteria which, in itself, was a major milestone in recent history of our understanding of the illness (Sharpe et al., 1991).
The report then considered other salient issues highlighted as barriers to conceptual conformity in CFS research. In order to minimise sampling bias, the guidelines proposed randomisation or consecutive referral as the preferred methods of patient selection. The need for both cross-sectional and longitudinal study designs was also encouraged: 'the former (cross-sectional) to establish associations; and the latter (longitudinal) to demonstrate temporal sequence (e.g. of infection and symptoms)' (p. 119). Finally the report stressed the need for reliable, valid and reproducible measures to assess the illness: 'Reliable measures of subjective fatigue and of disability are lacking and require development' (p. 120).

The 1991 consensus report provided a structured method for categorising CFS and produced coherent guidelines for both clinicians and researchers in the field. The contributors’ expectation: ‘to provide a basis for fruitful research studies and for inter-disciplinary collaboration essential to this field of research’ (p. 121), were fulfilled in the years that followed.

The lack of scientific evidence to suggest a possible cause coupled with the distinct absence of a physical diagnostic tool has prompted reluctance by certain sections of the medical profession to accept CFS as a bona fide illness. As the gatekeepers to the wider medical profession, General Practitioners (GPs) have the power to grant or deny patients access to specialist care solely depending on their particular view point. Practitioners sceptical about CFS would, for example, be less likely to refer patients to secondary care than those more receptive to such illnesses.

Anecdotal accounts from the CFS outpatient clinic in Cardiff uncovered a pattern to the course interviews between patients and their GPs took when the illness first began manifesting itself. Firstly, patients reported that the doctor would initially carry out physical examinations and a variety of blood tests. As time went on, with test results
showing no organic cause for their illness, GPs began to insist that “there is nothing wrong with you”, with the inference often being that the patient should “pull themselves together” or “just go out and enjoy yourself, try to forget about it”. By expressing doubt on the very existence of the illness and an obvious lack of awareness of specialised knowledge, GPs were perpetuating a breakdown in any relationship occurring between patient and doctor.

In an attempt to rectify this, the English Chief Medical Officer (CMO) established a Joint Working Group Committee between the Royal Colleges of Physicians, Psychiatrists and General Practitioners to inform medical opinion (Royal Colleges of Physicians, Psychiatrists and General Practitioners, 1996; Wessely, 1996). Members of the committee had working experience of CFS and the majority were actively involved in research. The committee was instructed to be guided by evidence-based medicine and for any recommendations made to be supported by published data together with clinical experience.

ii) Joint Working Committee of Royal Colleges of Physicians, Psychiatrists and General Practitioners

The committee considered that Chronic Fatigue Syndrome was the most appropriate term for the illness as: ‘This can be operationally defined, a prerequisite for clinical research. It is a short and accurate label, free from unproven aetiological claims’ (Wessely, 1996, p.498). The report went on to reject the term ME as it was believed that it: ‘erroneously endorses the existence of a specific pathology for which there is no evidence’ (p. 498). The committee agreed that there was no clear evidence to support the causative role of viral infections and, whilst accepting that EBV infection may result in chronic fatigue, agreed that the aetiology of CFS was multi-factorial (both physical and psychological). One key point made in the report included inconsistent reporting of the
cognitive impairments associated with the illness: ‘Further research should be encouraged into neurobiological aspects of CFS, using adequate case definitions, sample descriptions and assessment of confounders’ (p. 500). The report also set out a list of essential skills necessary for service providers including the need for rehabilitation programmes which were tailored to the needs of the patient and delivered by members across a range of disciplines. Recommendations were also made that healthcare providers should: ‘remain informed about current evidence on CFS’ (p. 504). The committee expressed the belief that the majority of cases should be managed in primary care and stressed the importance of the doctor-patient relationship.

The Joint Working Group report was not well received by some patients, carers and voluntary organisations. This was mainly due to the dismissal of the term ME by the Royal Colleges and, what was considered by some, an over-emphasis of the psychological aspects of the illness. This led to the CMO commissioning a new Working Group in 1998. The CFS/ME Working Group was made up of representatives from healthcare professionals, academics, patients, carers and support groups.

iii) The CFS/ME Working Group

The CFS/ME Working group were given the brief to: ‘review management and practice in the field of CFS/ME with the aim of providing best practice guidance for professionals, patients and carers to improve the quality of care and treatment for people with CFS/ME’ (CFS/ME Working Group, 2002, p. 2). The Working Group considered that there were five areas that needed to be addressed with some urgency. First was the recommendation that NHS and healthcare professionals should recognise the existence of the illness and that the terminology used to describe it should be reviewed. Next was the recommendation that all healthcare professionals should have the knowledge, awareness and understanding required to assess, manage and support patients. The
The report went on to specify the direction of future research highlighting six areas of importance including aetiology and pathogenesis of the illness together with its epidemiology and natural history, the identification of characteristics and/or subgroups, the assessment of potential therapeutic interventions (including symptom control) and the development of appropriate outcome measures for clinical and research use. The final area of research highlighted by the report was the need for further investigation of the efficacy (and cost-effectiveness) of different models of care. Although the Working Group acknowledged that there was no cure available for sufferers with CFS, it identified three possible management options – Cognitive Behaviour Therapy (CBT), graded exercise and pacing. In graded exercise a therapist aims to, work with the co-operation of the patient, gradually increase activity. The term pacing is used to describe a method by which the sufferer strikes a balance between activity and rest in order to conserve energy. Comparisons between the benefits of counselling and these three rehabilitative approaches were also recommended (CFS/ME Working Group, 2002).

The Working Group report, although wide ranging, appeared to suggest that scientific knowledge around CFS had not advanced a great deal since the Oxford consensus meeting had produced their guidelines in 1991 (Sharpe et al., 1991). Similarly, the
implication was made that illness management and the way in which patients were viewed by healthcare professionals had not changed in light of the 1996 report (Royal Colleges of Physicians, Psychiatrists and General Practitioners, 1996). However, this report also courted controversy and publication was delayed when four key group members (two psychiatrists, a public health doctor and a nurse therapist) resigned. The four members stated that they had resigned because: ‘the report plays down the psychological and social aspects of the condition and concentrates on a medical model’ (Eaton, 2002a, p. 7). They also expressed concern at the inclusion of pacing as a form of treatment as it had not been tested under trial conditions. In fact, ten people in total resigned from the Working Group during compilation of the report. The recommendation that CBT and graded exercise should be used in management programmes prompted the resignation of two patient representatives (Eaton, 2002b). Following publication of the report, further concerns were voiced about the use of the compromise term CFS/ME (Sharpe, 2002) and it was deemed by some that the report’s conclusions appeared: ‘more shaped by anecdote than evidence’ (Straus, 2002, p. 124).

Despite the controversy caused, a major positive outcome from the 2002 CMO report was the announcement by the Government that an £8.5 million investment was to be made in order to develop clinical services for patients with CFS in the UK.

In conclusion, Chronic Fatigue Syndrome in its many different forms has caused much consternation to the medical profession, researchers, sufferers and, more recently, health service policy makers alike. The illness, where the fatigue experienced is excessive, chronic and unresolved by rest or sleep, has no apparent cause, clinical diagnosis or indeed cure.
The meeting of experts in Oxford found that the discord evident in previous research into the illness could be attributed to several methodological flaws. A set of guidelines were developed that facilitated comparability between studies and provided a platform from which research in the UK could develop. Those present further concluded that there was a need to identify and investigate factors responsible for both causing the illness and also perpetuating it. The guidelines did not aim to influence the nature of research (by entering the ‘organic versus psychological cause’ debate) but rather to provide the means by which further discord between study findings could be prevented. The group also developed a working case definition which provided a gold standard for researchers to use when describing patients suffering from CFS (Sharpe, et al., 1991).

The Royal Colleges report, although not popular with all, agreed the term Chronic Fatigue Syndrome and recommended that all clinicians accept the existence of the illness. The Joint Working Committee concluded that too many practitioners were failing to provide a service for patients with the illness and recommended that physicians should take steps to manage patients in their care. The report stated that: ‘No patient should feel that their credibility is being doubted. There is no place in the clinical consultation for such statements as ‘there is nothing wrong with you’ or ‘it is all in the mind’, just as there is no place for such statement as ‘you have ME – there is nothing I can do’” (Wessely, 1996, p. 501). The illness, it was concluded, would be better managed by multi-disciplinary healthcare teams.

The CFS/ME Working Group, whilst acknowledging the absence of a cure, concluded that CBT and graded exercise provided the most successful methods for managing symptoms of the illness to date. This consensus appeared in accordance with results arising from several treatment trials conducted in England (Deale, et al., 1997; Fulcher & White, 1997; Sharpe, et al., 1996). The Working Group also repeated the Royal Colleges
call for the development of multi-disciplinary teams of healthcare professionals offering individualised treatment programmes designed to best suit the patients' needs.

This section of the critical analysis has endeavoured to draw attention to the problems chronic unexplained fatigue has presented to medicine and the steps taken by clinicians and researchers to resolve them. The Cardiff CFS Project developed as a direct result of the 1991 Guidelines and from the start aimed to realise one of the prime objectives from the report – namely to investigate and identify a range of factors associated with the illness. Research into CFS at this time was broadly split into two camps – those investigating organic basis and causes and those investigating the psychological aspects of the illness. Throughout the duration of the Cardiff project a number of measures were developed in an attempt to quantify impairment within the patient sample. It quickly became apparent that these same measures could be utilised as evaluation tools in recovery and possible treatments.

The following section describes the ways in which the recommendations from the three reports outlined above were realised within the Cardiff CFS Project.
2 Aims and Objectives

2.1 Aims

There were two overarching aims of the research which set out to increase the CFS evidence base, namely:

1. To conduct an in-depth investigation into a range of factors associated with and responsible for perpetuating CFS and thereby describe the natural progression of the illness (Linbury Trust project)

2. To investigate patient and practitioner education and evaluate possible treatment vehicles (Gatsby Foundation project)

2.2 Objectives

1. Documenting preliminary findings of the cognitive impairments associated with CFS and the effect of acute fatigue on them (Paper 1)

2. Investigating the role of sleep abnormalities (Paper 2) and upper respiratory tract infections (Paper 3) in the perpetuation of the illness

3. Evaluating evidence to support findings implicating the role of mood disorders, psychosocial factors and illness behaviours in CFS and to describe the cognitive deficits associated with it (Paper 4)

4. Investigating factors which might work together to perpetuate the illness and exert an effect on outcome and to describe recovery in the untreated patient (Paper 5)

5. Identifying patient characteristics associated with successful treatment outcomes and in doing so developing a strategy for evaluating healthcare provision (Papers 4, 5 & 6)
6. Documenting the level of patient education and General Practitioner (GP) knowledge (Paper 7)

7. Evaluating and comparing possible treatment strategies (Papers 8, 9 & 10)
3  The Manuscripts for Submission of PhD by Published Works

Paper 1: Acute fatigue in Chronic Fatigue Syndrome

Paper 2: The relationship between subjective ratings of sleep and mental functioning in healthy subjects and patients with Chronic Fatigue Syndrome

Paper 3: Chronic Fatigue Syndrome and susceptibility to upper respiratory tract infections

Paper 4: An investigation into the cognitive deficits associated with Chronic Fatigue Syndrome

Paper 5: Measuring recovery in Chronic Fatigue Syndrome patients and assessing the impact of associated risk factors on positive outcome

Paper 6: An investigation of the long term benefits of antidepressant medication in the recovery of patients with Chronic Fatigue Syndrome

Paper 7: Primary healthcare provision and Chronic Fatigue Syndrome – a survey of patients’ and practitioner’ beliefs

Paper 8: The evaluation of counselling and rehabilitation courses for Chronic Fatigue Syndrome patients

Paper 9: The effect of Multi Convergent Therapy on the psychopathology, mood and performance of Chronic Fatigue Syndrome patients – a preliminary study

Paper 10: A multi-convergent approach to the rehabilitation of patients with Chronic Fatigue Syndrome – a comparative study
Acute fatigue in chronic fatigue syndrome patients

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ABSTRACT

Background. Chronic fatigue syndrome (CFS) patients often complain that they are more susceptible to acute mental fatigue. It is important to determine whether this is observed using objective tests of sustained attention and responding.

Methods. Sixty-seven patients who fulfilled the criteria for CFS proposed by Sharpe et al. (1991) were compared with 126 matched healthy controls. Acute fatigue was assessed by comparing performance at the start and end of a lengthy test session and by examining changes over the course of individual tasks.

Results. CFS patients showed impaired performance compared to the controls and these differences increased as the volunteers developed acute fatigue. In addition, differences between the two groups were larger at the end of the test session.

Conclusions. The present results show that CFS patients are more susceptible to acute fatigue than healthy controls. This could reflect motor fatigue or an inability to compensate for fatigue with increased effort. This profile is consistent with previous research on fatigue and suggests that interpretation of certain aspects of CFS may be helped by considering it as the end point of a continuum of fatigue rather than a distinct disease.

INTRODUCTION

A number of syndromes have been described that refer to patients who present with the principal complaint of disabling fatigue. The term 'chronic fatigue syndrome' (CFS) is the most frequent name used for these conditions, largely because it is descriptive and free from aetiological implications. Behavioural abnormalities are a common feature of CFS, with patients often reporting the following problems: mental fatigue; psychiatric symptoms such as depression; sleep disturbance; and impairments of attention, memory and psychomotor functioning.

There is a general consensus that CFS patients do report more cognitive problems than controls. Smith (1991) compared 200 patients and 100 healthy controls and found that the CFS patients reported more cognitive failures (measured using the cognitive failures questionnaire, Broadbent et al. 1982). Similarly, Smith et al. (1993a) found that 84% of their sample of CFS patients complained of loss of concentration and 68% of memory problems. These results have been confirmed by considering problems associated with specific tasks (e.g. reading—Wearden & Appleby, 1997) and by asking about the extent to which the patients had to cease activities involving mental work (Wood et al. 1994).

A different picture emerges when one considers results from studies using objective tests of mental functioning. Several studies have found subjective reports of cognitive impairments but little (if any) decrement on objective tests (Altay et al. 1990; Grafman et al. 1993; Ray et al. 1993; Wood et al. 1994). Other studies have found significant impairments, although
the precise nature of these has been variable (Deluca et al. 1993, 1995; Sandman et al. 1993; Smith et al. 1993a). These conflicting results probably reflect several things. First, patient selection has varied considerably as has the choice of control groups. Secondly, important variables, such as pre-morbid intelligence have not been controlled for in some studies. Thirdly, some studies have lacked experimental power and others have not considered possible confounders in the analyses. Finally, tasks used have varied from those sensitive to structural changes to those which are known to be sensitive to changes in physiological state. One possibility is that at least some of the impairments seen in CFS patients are similar to those observed in healthy individuals who are suffering from acute fatigue. This view suggests that tests known to be sensitive to low arousal states (e.g. sleep deprivation) should also be impaired in CFS patients. Indeed, such results would be consistent with the view that CFS represents the end point of a fatigue continuum (from acute to chronic fatigue to CFS) rather than a distinct condition.

Evidence for the above view comes from two types of study. First, Smith et al. (1996) examined the role of sleep disorder in CFS. They found that the problems of memory and attention seen in CFS were restricted to those with sleep disorder (and that similar impairments were seen in the controls with sleep problems). Given that sleep disorders are frequently observed in CFS patients (Moldovsky, 1993; Farmer et al. 1995) it is clearly worthwhile considering the extent to which performance impairments in CFS resemble those induced by sleep deprivation.

Acute fatigue may also be induced by viral infections and following some types of infection (e.g. influenza, glandular fever) this fatigue may persist for weeks or even months (White et al. 1995). Smith (1992) reports a study comparing 25 CFS patients, 32 healthy controls and 10 patients with fatigue following confirmed influenza illnesses in the previous month. These groups were well-matched for age and pre-morbid intelligence and the results showed that both CFS and influenza groups were impaired on free recall, recognition memory and selective and sustained attention tasks compared to the control group. Hall & Smith (1996) used similar tests to examine after-effects of infectious mononucleosis. The results showed that selective impairments of memory and attention were apparent 6 months after the original illness. This again suggests that performance impairments seen in CFS may be similar to those produced by short-term or chronic fatigue.

There is considerable evidence that when a person is fatigued they are more sensitive to other factors which lower arousal (see Tilley & Brown, 1992, for a review). For example, sleep deprived individuals show greater decrements when tasks are long and monotonous than the non-deprived people. Similarly, if a task requires a great deal of effort fatigued individuals will not be able to compensate for their lowered alertness for long periods and impairments will start to show. The main aim of the present study was to determine whether CFS patients are more susceptible to acute fatigue than controls. If this is the case it may be extremely useful to view CFS as an end point on a fatigue continuum.

It should be pointed out at this stage that the conceptualization of CFS described above cannot account for all features of the disease. Indeed, the results from the studies described in the previous section (Smith, 1992; Hall & Smith, 1996; Smith et al. 1996) all showed that CFS patients had a motor slowing that could not be accounted for by sleep problems and which was not observed in short-term post-viral groups. This motor slowing could reflect physical deconditioning and this problem probably needs to be considered separately from the cognitive aspects of the syndrome.

Prolonged work leads to identical problems to those induced by sleep disturbance or other methods of producing acute fatigue. The vast literature on sleep deprivation and fatigue is, therefore, highly relevant to cognitive impairments in CFS. Acute fatigue may be indicated by lapses of attention but with more complex skilled performance the effect of fatigue is to disturb the essential timing, to impair memory for recently acquired information and influence selective attention (Craig & Cooper, 1992). Observed effects may depend on the personality or coping style of the person and also on task demands. The effects of fatigue become accentuated with time on task and in tasks which require continuous effort. One might predict, therefore, that CFS patients will show greater impairments as tasks progress especially...
3.1 Paper 1

Acute fatigue in CFS patients

if they involve continuous responding. The following study was designed to test this view.

METHOD
Participants
Chronic fatigue syndrome patients
The study examined patients with CFS, as defined by the Oxford criteria (Sharpe et al. 1991). Patients were recruited from the primary health care setting by standard NHS referral. All subjects attending the clinic were invited to attend the Health Psychology Research Unit (HPRU) based at the University of Wales College of Cardiff for a testing session. Subjects were aware that their participation was entirely voluntary. Of the first 100 patients attending the clinic, 67 agreed to make part in the present study and details about them are given in the first part of the Results section. Non-participation usually reflected the fact that the patients lived too far from Cardiff. Indeed, only six of the 100 actually refused to participate in any research. Questionnaire measures (see later section) showed no differences between patients who did and did not take part in the study.

Control group
One hundred and twenty-six members of the general population were recruited to take part in the study as control subjects for a chronic fatigue sample. These subjects were recruited from an advertisement in the local press and selected to participate on the basis of age and occupational status.

Procedure
Information about the patients and controls was initially collected by questionnaire. The information ranged from standard demographic details to measures of physical and mental health and cognitive functioning. These questionnaires are listed in Table 3.

The volunteers then attended for a single session in the laboratory. Performance was assessed over a period of about 2 h and the volunteers carried out computerized tests measuring a variety of aspects of memory, attention and psychomotor function.

Acute fatigue was assessed in two ways. First, two tasks were completed at the start and then again at the end of the test session. Differences between the start and end tests would act as a general indicator of fatigue over the session. Secondly, it was possible to analyse some tasks minute by minute, which meant that one could look at the build up of fatigue over specific tasks. The tasks selected were those which have been shown to be sensitive to sleep loss and other forms of acute fatigue (see Craig & Cooper, 1992; Smith & Maben, 1993) and to be impaired in CFS patients (Smith, 1992; Smith et al. 1993b).

All computer tasks were performed using an Amstrad PC1640 computer. Responses were measured using a Coliglog response box connected to a timer card allowing measurement of reaction times to the nearest millisecond. The box was designed to offer all the keys required to complete the tasks. These keys comprised three white square buttons, the central one being used in the simple reaction time tests, and the buttons either side were used when subjects performed forced-choice tasks. These keys facilitated measurement of responses and reaction times. There were also a set of red keys which could be illuminated and were used in the five-choice task.

Details of the tasks
Variable force-period simple reaction time task
In this task a box was displayed on the screen and this was followed after a period of 1–8 s by a square (the target) being presented in the middle of the box. The subject had to press a key as soon as the square was detected and, following this, another box was presented. This task lasted for 3 min.

Fixed fore-period simple reaction time task
This was identical to the above task except that the time between the box being displayed and the box appearing was always 2 s.

Five-choice serial response task
Five key-lights were displayed on the response box and when a light appeared in one of the keys the subject had to press the appropriate key and then a central home key. The next light was then displayed, and so on. This task measured the speed and accuracy of self-paced serial responding; it lasted for 3 min.
3.1 Paper 1

Detection of repeated numbers
Subjects were shown three-digit numbers on the screen at the rate of 100 per min. Normally each stimulus differed from the previous one but occasionally the same number was repeated on successive trials. The subjects had to detect these repeats and press the keyboard as soon as they appeared; the task lasted for 3 min.

Logical reasoning task
Subjects were shown statements about the order of the letters A and B followed by the letters AB or BA (e.g. A follows B BA). The subjects had to read the statement and decide whether it was a true description of the order of the letters. If it was the subject pressed the T key on the keyboard, if it was not they pressed the F key. The sentences ranged in syntactic complexity from simple active to passive negative (e.g. A is not followed by B). Subjects completed as many as possible in 3 min.

RESULTS

Description of participants
The groups did not differ in terms of age, gender, social class or pre-morbid intelligence (CFS: 47 females, 20 males; mean age females = 43.5 years, range 17–73; mean age males = 39.7 years, range 17–63; 33.3% single, 59.1% married, 61% divorced; pre-morbid intelligence NART mean correct score = 37.53, s.d. = 7.2. Controls: 83 females, 43 males; mean age females = 40.4 years, range 21–79 years; mean age males = 39.1 years, range 21–66 years; 32.5% single, 50.8% married, 15.5% divorced; pre-morbid intelligence NART mean correct score = 37.52, s.d. = 7.9).

Profile of the patients
Reported aetiology
The HPRU chronic fatigue patients reported a range of precipitating factors with 95.5% of patients reporting a precipitating factor for their illness. These factors (not mutually exclusive) ranged from influenza (41%), a sore throat (32%), glandular fever (27%), stomach upset (14%) and stress (41%). These are the standard factors recalled by CFS patients, which confirms the similarity of the present sample with those described in other specialist clinics.

Table 1. Symptom checklist (percentage reporting each symptom) and statistical difference between groups

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Controls %</th>
<th>Chronic fatigue %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical weakness</td>
<td>7.9</td>
<td>8.6</td>
<td>**</td>
</tr>
<tr>
<td>(50% more than before you were ill)</td>
<td>10.3</td>
<td>9.0</td>
<td>**</td>
</tr>
<tr>
<td>Excessive fatigue</td>
<td>4.8</td>
<td>11.8</td>
<td>**</td>
</tr>
<tr>
<td>(50% more than before you were ill)</td>
<td>27.8</td>
<td>89.4</td>
<td>**</td>
</tr>
<tr>
<td>Headache</td>
<td>7.5</td>
<td>15.7</td>
<td>**</td>
</tr>
<tr>
<td>Muscle pain in back, arms or legs</td>
<td>2.4</td>
<td>3.9</td>
<td>**</td>
</tr>
<tr>
<td>Pain in chest</td>
<td>11.9</td>
<td>25.9</td>
<td>*</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.8</td>
<td>14.3</td>
<td>**</td>
</tr>
<tr>
<td>Indigestion</td>
<td>11.9</td>
<td>25.9</td>
<td>*</td>
</tr>
<tr>
<td>Bloated stomach</td>
<td>14.3</td>
<td>40.9</td>
<td>**</td>
</tr>
<tr>
<td>Skin rash</td>
<td>12.7</td>
<td>42.5</td>
<td>**</td>
</tr>
<tr>
<td>Sore throat</td>
<td>7.9</td>
<td>47.0</td>
<td>**</td>
</tr>
<tr>
<td>Headache</td>
<td>11.9</td>
<td>66.7</td>
<td>**</td>
</tr>
<tr>
<td>Earache</td>
<td>1.6</td>
<td>24.2</td>
<td>**</td>
</tr>
<tr>
<td>Sore eyes</td>
<td>18.3</td>
<td>56.1</td>
<td>**</td>
</tr>
<tr>
<td>Sensitive to noise</td>
<td>5.6</td>
<td>65.2</td>
<td>**</td>
</tr>
<tr>
<td>Sensitive to light</td>
<td>11.1</td>
<td>63.6</td>
<td>**</td>
</tr>
<tr>
<td>Feeling hot/cold</td>
<td>9.5</td>
<td>73.3</td>
<td>**</td>
</tr>
<tr>
<td>Sweating</td>
<td>8.3</td>
<td>45.5</td>
<td>**</td>
</tr>
<tr>
<td>Shivering</td>
<td>9.7</td>
<td>45.5</td>
<td>**</td>
</tr>
<tr>
<td>Swollen glands</td>
<td>3.2</td>
<td>42.4</td>
<td>**</td>
</tr>
<tr>
<td>Racing heart</td>
<td>4.8</td>
<td>31.8</td>
<td>**</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10.3</td>
<td>45.5</td>
<td>**</td>
</tr>
<tr>
<td>Depression</td>
<td>10.3</td>
<td>39.4</td>
<td>**</td>
</tr>
<tr>
<td>Anxiety/Panic feelings</td>
<td>9.5</td>
<td>31.8</td>
<td>**</td>
</tr>
<tr>
<td>Loss of concentration</td>
<td>15.4</td>
<td>80.4</td>
<td>**</td>
</tr>
<tr>
<td>Loss of memory</td>
<td>8.7</td>
<td>80.3</td>
<td>*</td>
</tr>
<tr>
<td>Allergies</td>
<td>14.3</td>
<td>30.3</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01.

Illness duration
Patients reported an average illness length of 62.75 months with an average diagnosis length of 24 months.

Current severity
A self-assessment of the current state of their illness showed the following results: worse than at any stage of the illness, 61.1%; bad, 24.2%; bad with some recovery, 42.4%; recovering with occasional relapses, 27.3%; and almost completely recovered, 0%.

Symptom checklist at time of testing
A symptom check-list used in previous studies of chronic fatigue patients (Smith et al. 1993a) and measuring symptoms commonly reported by these patients (Komaroff, 1994) was administered. The percentage of patients and controls reporting various symptoms typically associated with CFS is shown in Table 1. The
patients differed from the controls for all symptoms and the results correspond well with those obtained in other studies (Smith et al. 1993a).

### Sleep

Generally, the CFS patients reported an increase in sleep disorders with 80% rating the quality of their sleep as worse than before their illness onset. Statistical analyses, using t tests, showed that the patients rated the quality of their sleep as worse than the controls ($P < 0.01$) and reported more problems getting to sleep ($P < 0.05$) and awakening early ($P < 0.01$). In terms of duration of sleep, there was no difference in the mean duration of the two groups but CFS patients were more likely to be very short or long sleepers than the controls.

### Questionnaire scores for patients and controls

These scores are shown in Table 2. The patients reported more problems of physical health, mental health and more cognitive impairments than the controls. All of these differences were highly significant (based on t tests) and apparent in all the specific measures.

### Performance

Analyses of variance were carried out on the performance data distinguishing the between subject factor of patients/controls and the within subject factor of session or time on task. Levene's tests were conducted to test for normality and if this was not the case an appropriate transformation was obtained using Box-Cox diagnostic plots.

#### Tests at the start and end of the session

**Variable fore-period reaction time task**

A two-way analysis of variance (logarithmic data) was performed comparing variable reaction time tasks performed at the beginning and the end of the test session. The analysis showed significant effects of group ($F = 76.2$, $df = 1,183$, $P < 0.01$) showing patients to be slower than controls. There was also a significant effect of test repeat ($F = 136.65$, $df = 1,183$, $P < 0.01$) showing both groups to be slower at test 2. The interaction between groups and test was not quite significant ($P > 0.05$), although the patients showed greater slowing over time (mean reaction in ms with s.d. in parenthesis: CFS – first test, 422 (209); second test, 495 (230); difference between test 2 and test 1 = 73 and Controls – first test, 284 (51); second test, 325 (63); difference between test 2 and test 1 = 44).

**Logical reasoning task**

A two-way analysis of variance of the completed tasks looking at patients and controls for the first and second test showed a significant difference between groups ($F = 4.3$, $df = 1,184$, $P < 0.05$) and a significant difference between test sessions ($F = 163.69$, $df = 1,184$, $P < 0.01$). The interaction between group and test session just failed to achieve significance ($F = 3.44$, $df = 1,184$, $P > 0.05$). The results showed that controls completed more trials than patients and

---

### Table 2. Questionnaire measures of physical and mental health and cognitive problems

<table>
<thead>
<tr>
<th></th>
<th>CFS Mean (s.d.)</th>
<th>Controls Mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Profile of fatigue related symptoms</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>63.0 (12.4)</td>
<td>224 (11.2)</td>
</tr>
<tr>
<td>Somatic symptoms</td>
<td>49.7 (18.0)</td>
<td>254 (8.8)</td>
</tr>
<tr>
<td>Emotional distress</td>
<td>46.2 (18.6)</td>
<td>325 (15.7)</td>
</tr>
<tr>
<td>Cognitive difficulty</td>
<td>49.9 (12.1)</td>
<td>254 (10.6)</td>
</tr>
<tr>
<td>Cohen-Hoberman Index</td>
<td>244 (78)</td>
<td>64 (98)</td>
</tr>
<tr>
<td>of physical symptoms&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive failures questionnaire&lt;sup&gt;3&lt;/sup&gt;</td>
<td>608 (17.1)</td>
<td>38.3 (13.0)</td>
</tr>
<tr>
<td>State anxiety&lt;sup&gt;4&lt;/sup&gt;</td>
<td>410 (98)</td>
<td>319 (83)</td>
</tr>
<tr>
<td>Beck Depression Inventory&lt;sup&gt;5&lt;/sup&gt;</td>
<td>144 (6.6)</td>
<td>74 (6.3)</td>
</tr>
<tr>
<td>Mood last week&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative mood</td>
<td>239 (10.9)</td>
<td>141 (96)</td>
</tr>
<tr>
<td>Positive mood</td>
<td>264 (8.9)</td>
<td>369 (96)</td>
</tr>
<tr>
<td>Perceived stress scale&lt;sup&gt;7&lt;/sup&gt;</td>
<td>269 (8.4)</td>
<td>226 (86)</td>
</tr>
</tbody>
</table>

<sup>1</sup> Ray et al. (1992); <sup>2</sup>Cohen & Hoberman (1983); <sup>3</sup> Broadhead et al. (1982); <sup>4</sup>Spielberger et al. (1971); <sup>5</sup>Beck et al. (1961); <sup>6</sup>Zeeve & Tellegen (1983); <sup>7</sup>Cohen & Williamson (1988).

### Table 3. Changes with time on task

<table>
<thead>
<tr>
<th></th>
<th>Minute 1 Mean (s.d.)</th>
<th>Minute 2 Mean (s.d.)</th>
<th>Minute 3 Mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple reaction time task (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFS</td>
<td>391 (190)</td>
<td>397 (198)</td>
<td>434 (216)</td>
</tr>
<tr>
<td>Controls</td>
<td>230 (69)</td>
<td>257 (90)</td>
<td>258 (78)</td>
</tr>
<tr>
<td>Five choice serial response task (number done)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFS</td>
<td>91 (27)</td>
<td>95 (29)</td>
<td>93 (29)</td>
</tr>
<tr>
<td>Controls</td>
<td>121 (21)</td>
<td>130 (21)</td>
<td>130 (22)</td>
</tr>
<tr>
<td>Repeted digits detection task</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction times (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFS</td>
<td>555 (114)</td>
<td>534 (109)</td>
<td>655 (167)</td>
</tr>
<tr>
<td>Controls</td>
<td>527 (102)</td>
<td>545 (114)</td>
<td>578 (135)</td>
</tr>
<tr>
<td>Hits (% correct)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFS</td>
<td>56.5 (22)</td>
<td>49.6 (27)</td>
<td>36.2 (23)</td>
</tr>
<tr>
<td>Controls</td>
<td>66.4 (21)</td>
<td>61.8 (22)</td>
<td>43.8 (23)</td>
</tr>
</tbody>
</table>

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3.1 Paper 1
that performance for both groups improved in the second test, although the improvement was greater for the controls (mean number completed with, s.d. in parenthesis: CFS - first test, 32/4 (11·3); second test, 39·1 (12·8); difference between test 2 and test 1 = 6·7; and Controls - first test, 36·4 (12·6); second test, 44·6 (14·0); difference between test 2 and test 1 = 8·3).

There were no significant effects in the analysis of the accuracy data (mean percentage correct with, s.d. in parenthesis: CFS - first test, 74·6 (20·2); second test, 76·5 (19·0); difference between test 2 and test 1 = 19·9% and Controls - first test, 78·1 (19·4); second test, 78·4 (18·4); difference between test 2 and test 1 = 0·4%).

**Time on task effects**

**Simple reaction time task**

The reaction times for each minute of this task are shown in Table 3. The data were logarithmically transformed and an analysis of variance showed significant differences between groups (F = 52·37, df = 1,186, P < 0·01) but no significant effect of time on task (F = 2·93, df = 2,372, P > 0·05). There was a significant interaction between group and time (F = 3·03, df = 2,372, P < 0·05). These results show that the CFS group were slower and that they showed greater fatigue in the last minute of the test.

**Five choice serial response task**

These data are shown in Table 3. An analysis of variance showed a significant effect of group (F = 91.77, df = 1,189, P < 0·01), a significant effect of time on task (F = 68·63, df = 2,378, P < 0·01) and a significant interaction of the two (F = 15·26, df = 2,378, P < 0·01). These results showed that patients consistently completed fewer trials than the controls, that rate varied over time for both patients and controls and that the difference in performance between patients and controls increased over time (minute 1, 30; minute 2, 35; minute 3, 37).

**Repeated digits task**

The reaction times to targets are shown in Table 3. The data were logarithmically transformed and the analysis of variance again showed a significant group × time on task interaction (F = 5·7, df = 2,344, P < 0·01) which reflected the much greater slowing of the CFS patients in the last minute.

The accuracy data (see Table 3) showed a highly significant difference between the CFS group and the controls (F = 11·05, df = 1,183, P < 0·01) and a highly significant effect of time on task (F = 74·6; df = 2,366, P < 0·01) but no interaction. The patients detected fewer targets than the controls, both groups showed a decline in performance with time on task, but the difference between patients and controls remained constant over time. This shows that accuracy was maintained by the patients but at the expense of slowing of response times in the last minute.

**DISCUSSION**

The main aim of the present study was to determine whether CFS patients were more sensitive to acute fatigue than a matched healthy control group. This was examined by comparing performance at the start and end of a lengthy test session and by considering changes over the course of tasks requiring sustained attention and/or sustained responding. All of the results supported the view that CFS patients are more susceptible to acute fatigue than controls, and the time on task analyses revealed significant interactions between CFS/controls and minutes doing the task. The profile of impairments is very similar to that obtained in sleep deprivation, where effects increase with time on task and are often observed in tasks involving sustained attention. Many of the effects could reflect an increase in motor fatigue, leading to slower response times. The ability to detect targets in a cognitive vigilance task did not show an increased difference between patients and controls over time whereas most of the speed measures did. This suggests that an explanation in terms of increased motor fatigue or reduced effort is plausible.

It is important to point out that differences between CFS patients and controls were present at the very start of the test session. In other words the groups differed initially but these differences became larger with increasing time on task. The initial impairments seen in the CFS group may reflect fatigue induced in ways other than prolonged work (e.g. sleep disturbance). Indeed, it is now desirable to determine whether CFS patients are generally more sensitive to all factors which reduce arousal. For example, one might predict that they would be especially impaired when their circadian arousal is low.
Similarly, CFS patients with high extraversion score might be especially sensitive due to their generally low level of cortical activation.

One must also now consider whether the increased sensitivity to acute fatigue can be reduced. This could take two alternative forms. First, if it is the case that the acute fatigue effects reflects an underlying sleep disorder then pharmacological treatment may remove the effects reported here. A second approach would be to try to increase alertness to determine whether this stops the rapid build-up of fatigue. The problem with the second approach is that many of the methods used to change low arousal states could have specific as well as non-specific alerting effects on CFS patients. For example, noise can reverse effects seen in low arousal situations (Smith & Nutt, 1996) but many CFS patients report very high sensitivity to noise. Similarly, caffeine is remarkably effective in reducing fatigue (Smith et al. 1993b) but many CFS patients report negative effects from caffeine consumption. At the moment it is unclear whether any unwanted side effects will occur if drugs changing the turnover of central noradrenaline are given to CFS patients. If they do tolerate these compounds then there may be some reduction in their fatigue. Furthermore, if the drugs also contain compounds which change the serotonin system then further benefits (e.g. reduction of sleep problems) may be found. The methods used in the present study provide a means of testing these views.

Overall, there would appear to be some value in considering certain features of CFS to be extreme forms of the problems associated with acute fatigue. It has already been mentioned that there are other aspects of the syndrome which can be better interpreted in other ways (e.g. physical de-conditioning). The major issue for interpretation based on a fatigue continuum is why the fatigue persists in these patients. A simple view of how this might occur can be found in the literature on fatigue and performance. Craig & Cooper (1992) suggests that the nature and extent of the fatigue associated with performance may depend on characteristics of the person doing the tasks. Observed effects may depend on personality or coping style as much as on the task demands themselves. Similarly, the ability to recover from a fatiguing situation may be much more important for long term health than the acute response to it. Bartlett (1933) pointed out that fatigue is not likely to be a problem until normal rest and sleep do not lead to full recovery before the next set of demands. Indeed, the mechanism by which fatigue is retarded may well comprise an emotional component of the previous demand. Therapy must aim to break this cycle and the best way to do it may clearly vary from person to person. Furthermore, the methods of reducing acute fatigue that were outlined earlier will probably have little effect on the pathogenesis of the disease unless the general demands placed on the person are changed as well.

In summary, the present study has demonstrated that objective tests of sustained attention and responding show differences between CFS patients and healthy controls. The size of these differences increases as the volunteers become more fatigued. This could either reflect motor fatigue or a reduction in effort with time on task. These results are consistent with results from previous studies of acute fatigue and suggest that understanding of some aspects of CFS may be enhanced by considering it as the end point of a fatigue continuum. Susceptibility to acute fatigue may be a good method of assessing a patient’s current state. Similarly, recovering from fatigue may be a very good indicator of the patients’ condition and the efficacy of treatments.

The research described here was supported by the Linbury Trust.

REFERENCES


The Relationship Between Subjective Ratings of Sleep and Mental Functioning in Healthy Subjects and Patients with Chronic Fatigue Syndrome

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The present study examined the relationships between subjective reports of sleep and mental functioning. This was done both for healthy subjects and chronic fatigue syndrome patients, a group who frequently report sleep disorders. Sleep abnormalities were found to be related to personality and to state measures of physical and mental health. Distractability, as measured by the Stroop task, was also related to sleep disorder. The psychomotor slowing observed in the chronic fatigue syndrome patients was not modified by sleep status. However, the problems of memory and sustained attention found in the patients were restricted to those subgroups with sleep disorders.

KEY WORDS—sleep, personality, mental and physical health, performance, chronic fatigue syndrome

INTRODUCTION

The relationship between sleep and mental performance and mood has been examined in a large number of sleep deprivation studies (see Tilley and Brown (1992) for a review). In general, the results from such experiments show that sleep deprivation is associated with increases in lapses of attention. Other impairments may be apparent if the tasks are demanding or have a large working memory component. These reflect the reduced level of alertness produced by sleep deprivation and the increased propensity to take microsleeps. Factors which increase arousal (e.g. exposure to loud noise) reduce the effects of sleep deprivation, where, as further decreases in arousal (e.g. due to fatigue or boredom) lead to even greater impairments. Recent work by Smith and Nutt (1996) has shown that these effects of sleep deprivation can be accounted for in terms of a reduction in central noradrenaline.

Other studies (reviewed by Campbell, 1992) have manipulated sleep patterns over longer periods (e.g. by reducing sleep by 2 h a night over several weeks). Such studies have usually shown no effect of changing sleep on performance. Another method of examining the relationship between sleep and behaviour is to record subjective reports of sleep duration, problems getting to sleep or early awakening. There is little information on how such measures relate to subjective well-being and mood and the primary aim of the present study was to provide preliminary data on this topic. In addition, the relationship between sleep and personality was examined so that it was possible to determine whether any effects reflected stable traits or abnormal states.

Chronic fatigue syndrome (CFS) patients were investigated along with matched healthy controls. This group were of interest in the present study for two reasons. First, sleep disorders are frequently observed in CFS patients (Moldofsky, 1993). Electrophysiological studies of sleep of chronic fatigue syndrome patients (Moldofsky et al., 1988; Whelton et al., 1992) have shown that they have more difficulty in falling asleep, spent less time asleep, have reduced REM sleep and greater alpha EEG activity during NREM sleep. Indeed, a formal psychiatric examination of 100 CFS patients and 50 healthy controls revealed that 79 per cent of the patients had sleep disorders compared with 44 per cent of the controls (DSM III R criteria, Farmer et al., 1995). A number of studies have shown that CFS patients have
increased psychopathology and impairments of psychomotor function, memory and attention (Smith, 1992; Smith et al., 1993; DeLuca et al., 1993; McDonald et al., 1993; Sandman et al., 1993). Other studies have failed to demonstrate such effects (e.g. Riccio et al., 1992), although these negative results may reflect use of insensitive tests or poor experimental power. Indeed, many of the tasks that have shown impairments in CFS patients are also sensitive to changes in state produced by fatigue or sleep deprivation. A second aim of the present study was to determine whether the behavioural abnormalities observed in CFS reflect sleep disorders or are still apparent even in patients with no sleep problems.

METHOD

Recruitment of the CFS patient and controls
Subjects were recruited from the chronic fatigue clinic, University of Wales College of Medicine. Patients were given a complete medical examination to exclude other medical conditions and routine laboratory assays conducted to assess any biochemical, haematological or immunological abnormalities. The patients also received a detailed psychiatric assessment. Patients who fulfilled the Oxford criteria for CFS (a syndrome characterized by fatigue as the principal component; a syndrome of definite onset that is not lifelong; fatigue that is severe, disabling and that is not lifelong; fatigue that has been present for at least 6 months during which it is present for more than 50 per cent of the time — Sharpe et al., 1991) were then asked to participate in the research. Sixty-seven of the first 100 patients from the clinic agreed to participate in the research programme and they then completed a series of questionnaires and carried out a battery of performance tests.

These patients were compared with 126 members of the general population who were recruited from an advertisement in the local press.

The demographic characteristics of the two groups are shown at the start of the results, as are the clinical characteristics of the patients.

Subjective assessment of sleep
Average sleep duration was recorded and subjects classified according to the distribution of the healthy controls. Normal sleep duration values were taken as those lying within one standard deviation of the mean. 'Mild sleep disorder' covered those values between 1 and 2 standard deviations from the mean and 'abnormal' sleep duration was taken to be greater than 2 standard deviations from the mean. Subjects were also classified according to whether they had problems going to sleep or woke up early (using a 'never', 'sometimes' and 'often' scale). A compound variable, degree of sleep abnormality, was derived from the above sleep variables. Six groups of subjects were created: patients/controls × normal, mild sleep disorder and abnormal sleep groups. (Patients: no sleep disorder N = 13; mild sleep disorder N = 27; abnormal sleep N = 24. Controls: no sleep disorder N = 42; mild sleep disorder N = 67; abnormal sleep N = 15).

Questionnaire and performance measures reported here
A large number of psychosocial measures and personality traits were assessed. Results from the Spielberger Trait Anxiety Inventory (Spielberger et al., 1971) are reported here as a typical example of what emerged from the analyses.

Similarly, state measures of physical and mental health were taken. The fatigue, somatic symptoms, emotional distress and cognitive difficulties scales of the profile of fatigue related symptoms (Ray et al., 1992) are reported here.

Previous studies have shown that CFS patients have slower psychomotor performance, poorer recall of a list of words, impaired sustained attention and are more distractable. Data from the five-choice serial response task, a free recall task, a cognitive vigilance task (all described in Smith et al., 1995) and the Stroop colour-word task (described in Smith and Broadbent, 1985) are reported here.

RESULTS

Demographics
The CFS patients consisted of 20 males (mean age: 39-6 years, range 17-63 years) and 47 females (mean age: 43-5 years, range 17-73 years). Of the patients, 59.1 per cent were married, 33.3 per cent single and 7.6 per cent divorced or widowed. The controls consisted of 43 males (mean age: 39-1 years, range 21-66 years) and 83 females (mean age: 40-5 years, range 21-79 years). Of the controls 50.8 per cent were married, 32.5 per cent single and
16.7 per cent divorced or widowed. The two groups did not differ in terms of socio-economic status. Similarly, they did not differ in terms of intelligence as revealed by scores from the NART (Nelson, 1976).

**Illness history, current symptoms of the CFS patients**

Patients reported an average illness duration of 62.8 months, although enormous individual variation was found (6–110 months). They rated their current severity on a 5-point scale and also completed a symptom check-list. These results are shown in Table 1.

| Table 1. Chronic fatigue patient sample: symptoms and current severity of illness |
|-----------------------------------|----------|
| Physical weakness (50% more than before you were ill) | 86.4% |
| Excessive fatigue (50% more than before you were ill) | 97.0% |
| Legs feeling heavy | 81.8% |
| Muscle pain in back, arms or legs | 89.4% |
| Pain in chest | 39.4% |
| Painful joints | 63.6% |
| Nausea | 48.5% |
| Indigestion | 25.0% |
| Bloating in stomach | 40.9% |
| Sore throat | 6.7% |
| Headache | 66.7% |
| Earache | 24.2% |
| Sore eyes | 56.1% |
| Sensitive to noise | 65.0% |
| Sensitive to light | 64.0% |
| Feeling hot/cold | 77.3% |
| Sweating | 45.5% |
| Shivering | 45.3% |
| Swollen glands | 42.4% |
| Racing heart | 31.8% |
| Insomnia | 45.3% |
| Depression | 39.4% |
| Anxiety/panic feelings | 31.8% |
| Loss of concentration | 89.4% |
| Loss of memory | 80.3% |
| Allergies | 30.3% |

*Subjective Ratings of Sleep*

The results show that although there was considerable variation in current severity the usual pattern of symptoms appeared to be present.

**Relationship between sleep scores and the questionnaire data**

(Degrees of freedom vary slightly from analysis to analysis due to missing data and/or the exclusion of outliers). Preliminary analyses were conducted to determine whether the sleep groups differed in terms of demographics. No significant effects were found. Similarly, the patients in the various sleep categories did not differ in terms of illness duration or severity.

**Trait anxiety.** Trait anxiety scores were significantly higher in the patients than controls ($F = 5.9$, $df = 1, 176$, $p < 0.02$). Sleep abnormality was also related to trait anxiety ($F = 6.35$, $df = 2, 176$, $p < 0.01$), with trait anxiety increasing with sleep disorder. These effects are shown in Figure 1. There was no significant interaction between patient/control groups and sleep.

**Fatigue.** Patients had significantly greater fatigue scores than the controls ($F = 385$, $df = 1, 178$, $p < 0.001$). Fatigue was also greater in subjects with sleep disorders ($F = 3.6$, $df = 2, 178$, $p < 0.05$) but the interaction between patients/controls and sleep was not significant. These results are shown in Figure 2, which show that all of the patient subgroups were more fatigued than the controls.

![Figure 1. Trait anxiety scores for CFS patients and controls in the various sleep categories. (Scores are the means: SDs shown as bars). NS, no sleep problems; M, mild sleep problems; AB, abnormal sleep](image-url)
Emotional distress. Emotional distress was greater in the patients than controls ($F = 12.1, df = 1, 180, p < 0.01$). It also increased with sleep abnormality ($F = 8.06, df = 2, 180, p < 0.01$) but the interaction between patients/controls and sleep group was not significant (see Figure 3).

Cognitive difficulty. Patients reported significantly higher levels of cognitive difficulty than controls ($F = 186.0, df = 1, 180, p < 0.05$). However, neither the difference between sleep groups nor patients/controls x sleep interaction were significant.

Somatic symptoms. The patients reported more somatic symptoms than the controls ($p < 0.01$) and those with abnormal sleep reported more symptoms ($p < 0.01$). Again, the interaction between patients/controls and sleep was not significant. These results are shown in Figure 4.

Overall, the results from the questionnaires show that the CFS patients have greater physical and mental health symptoms and that these symptoms increase if sleep is disturbed. However, no evidence of interactions between CFS/controls and sleep were significant suggesting that the effects of the disease and the sleep disorder are largely independent.

Relationship between sleep and measures of performance

Psychomotor speed: number done in the five-choice serial response task. The patients were significantly slower than the controls ($F = 68.1, df = 1, 180, p < 0.01$). Sleep had no effect and did not influence the difference between patients and controls (see Figure 5).

Free recall. Patients recalled fewer words than controls ($F = 5.4, df = 1, 182, p < 0.05$). There was also a significant interaction between CFS/controls and sleep ($F = 4.3, df = 2, 182, p < 0.05$) which is shown in Figure 6.

A Tukey's post-hoc test showed that it was only the patients with abnormal sleep who were worse than the controls.

Cognitive vigilance. Patients detected fewer targets than the controls ($F = 4.28, df = 1, 174, p < 0.05$).
3.2 Paper 2

SUBJECTIVE RATINGS OF SLEEP

![Graph 1](image1)

![Graph 2](image2)

![Graph 3](image3)

![Graph 4](image4)

There was also a significant interaction between CFS/controls and sleep (F = 3.09, df = 2, 174, p < 0.05) which is shown in Figure 7.

The results show that patients with no sleep disorder were not significantly different from the controls.

Stroop interference. The amount of interference from distracting stimuli was calculated by subtracting the time taken to name the patches of colour from the time taken to name the colour of the irrelevant words (e.g.: the word green printed in red, correct response = red). The results showed a significant main effect of sleep (F = 11.85, df = 2, 179, p < 0.01), with interference increasing in the abnormal sleep group (see Figure 8). Again, this shows that CFS patients with no sleep disorders are not more distractable by irrelevant stimuli.

DISCUSSION

This study has shown that subjective ratings of sleep are related to personality traits, state measures of physical and mental health and aspects of performance. CFS patients also differ from healthy controls on these measures. In the case of the subjective reports there was no evidence of interactions between CFS/controls and sleep disorder. This was also true in the case of psychomotor slowing, which was not influenced by sleep disturbance. The other performance tasks
showed that sleep disorder may be important in the impairments seen in the CFS group. In the case of free recall and sustained attention, impairments were not seen in the CFS/no sleep disorders subgroup. This was also true for the Stroop interference conditions, where sleep abnormality was the only significant effect.

These preliminary data clearly require replication. Similarly, other measures of sleep disorder need to be used to check that the results reported here are not specific to the particular scores derived here. It is also important to determine whether there is a causal relationship between sleep disorder and the other effects, or whether they merely are associated and reflect some other underlying mechanism. There is also the possibility that the effects attributed to sleep (or to differences between the CFS patients and controls) reflect some confounding factors. In the present study we have used well-matched groups and also (in unreported analyses) co-varied factors which could produce certain results (e.g. we have co-varied trait anxiety, which is influenced by sleep and differs in the CFS patients, and still found the same significant effects with the other measures). This approach leads us to believe that the effects reported here are robust.

Overall, the results show that sleep disorder, as measured by subjective report, is related to behavioural abnormalities. CFS patients have been shown to differ from controls and while the subjective reports reveal that this does not reflect problems with sleep, the objective performance tests show that problems of memory and attention are restricted to those patients with sleep disorders. These results have important implications for the study of sleep and the possible role of sleep disorder in the chronic fatigue syndrome.

ACKNOWLEDGEMENT

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REFERENCES


3.2 Paper 2

SUBJECTIVE RATINGS OF SLEEP


Chronic fatigue syndrome and susceptibility to upper respiratory tract illness

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Leszek Borysiewicz and Meirion Llewelyn
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Objectives. First, to determine whether chronic fatigue syndrome (CFS) patients report increased susceptibility to upper respiratory tract illnesses (URTIs) compared with healthy volunteers. Second, to determine whether symptom severity and use of medication is greater in CFS patients. Finally, to assess the impact of the URTIs on the subsequent clinical state of the patients.

Design. A 10-week diary study.

Methods. The frequency and severity of URTIs were recorded over a 10-week period by CFS patients (N = 62) and healthy controls (N = 44). The patients were selected according to the Oxford criteria and had previously been assessed at the Cardiff Chronic Fatigue Clinic. One group of patients and controls carried out the diary study from October to December, and another group from January to March. At the end of each of the 10-week periods the volunteers completed standard questionnaires about the frequency and severity of symptoms of colds and influenza and their general clinical condition.

Results. CFS patients reported more cold and influenza illnesses than the controls. The patients also reported greater symptom severity and use of medication for the URTIs; these differences were still observed when trait anxiety was covaried. There was little evidence of the URTIs leading to longer term changes in the primary symptoms of CFS.

Conclusions. CFS patients report more URTIs, greater symptom severity and greater use of medication for these illnesses than healthy controls. Further studies are now necessary to determine whether these results reflect greater susceptibility to infection or differences in symptom reporting. The present findings also suggest that acute infections do not play a major role in the pathogenesis of CFS.

A number of clinical syndromes have been described which refer to similar groups of patients who present with the principal complaint of disabling fatigue. Various names have been used to describe these diseases and the term 'chronic fatigue syndrome' (CFS) is now frequently used, largely because it is descriptive and free from aetiological

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implications. CFS is defined by 6 months of severe disabling fatigue that is made worse by physical or mental exertion, and for which no adequate medical explanation can be found. It is frequently associated with somatic symptoms such as myalgia, chest pain, headache and joint pain. Symptoms of depression and anxiety may be present and sleep disturbance is a common feature of the syndrome (joint working group of the Royal Colleges of Physicians, Psychiatrists and General Practitioners, 1996).

The role of viruses in the aetiology and perpetuation of CFS continues to be an area of debate. Several virus groups including herpesvirus, retroviruses and enteroviruses have been implicated in CFS, although none appear to be uniquely causative of the condition (Ablashi, 1994). The ideal method of studying aetiology involves prospective studies and these have shown that CFS can develop following glandular fever (White, Thomas, Amess, Grover, Kangro & Clare, 1993a,b) and viral meningitis (Hotopf, Noah & Wesseley, 1996) but not more common infections (Wesseley, Chalder, Hirsch, Pawlikowska, Wallace & Wright, 1995).

Other research has focused on the possibility that a persistent virus could be involved in the perpetuation of the disease. Recent molecular hybridization studies have suggested enteroviral involvement. For example, the presence of enteroviral sequences in muscle from CFS patients has been demonstrated in several studies. (Archard, Bowles, Behan, Bell & Doyle, 1988; Bowles, 1993; Cunningham, Bowles, Lane, Dubowitz & Archard, 1990). Similarly, using the polymerase chain reaction (PCR) technology, Clements, McGarry, Nairn & Galbraith (1995) and Galbraith, Nairn & Clements (1995) have suggested that about one-half of their CFS patients had a persistent enterovirus and that this was a distinct novel type. In contrast, other studies have found little evidence for the view that the pathogenesis of this syndrome depends on a persistent enteroviral infection (Gow, Behan, Simpsoll, McGarry, Keir & Behan, 1994; McCardle, McCardle & Jackson, 1996; Swanink et al., 1994). Indeed, the term 'enteroviral persistence' should not be used in connection with CFS as no one to date, has demonstrated unequivocally the presence of enterovirus nucleic acid sequences in serial samples from these patients.

An alternative interpretation of some of the CFS/enterovirus studies is that these patients are more susceptible to acute viral infections. This view is supported by several pieces of evidence. First, a number of studies have shown that psychological stress may increase susceptibility to infection (see Cohen & Williamson, 1991; Cohen, Tyrrell & Smith, 1991; Cohen, Tyrrell, Russel, Jarvis & Smith, 1993). CFS patients often report more negative life events, perceived stress, daily hassles and negative affect than healthy controls. This makes it plausible to suggest they might be more susceptible to infection. There is also some evidence that CFS patients have low natural killer cell activity and low production of interferon gamma and interleukin-2 (Straus, 1996), which could increase susceptibility to infection. Perhaps the strongest evidence that CFS patients show abnormalities of their anti-viral mechanisms comes from a study involving polio vaccine challenge (Vedhara et al., 1997). In this study the effect of live oral polio virus vaccination on CFS patients was examined in a double-blind study. Immunological and virological assays revealed differences between patients and controls: the CFS group showed increased polio virus isolation, earlier peak proliferative responses, lower T-cell subsets and a trend for reduced production of interferon gamma. However, the vaccine did not alter the clinical condition of the patients.

The aim of the present study was to determine whether CFS patients reported
increased susceptibility to upper respiratory tract illness (URTIs; colds and influenza) compared with a healthy group. There have been no previous studies of this topic and anecdotal reports of the incidence of URTIs in CFS are variable. A second aim of the study was to investigate whether symptom severity was greater in the CFS group. Finally, the impact of these acute illnesses on the primary symptoms of CFS was examined.

Method

Design
A 10-week diary study was carried out comparing the frequency and severity of URTIs in CFS patients and healthy controls. Patients had previously attended the Cardiff Chronic Fatigue Syndrome Clinic and were volunteers from the Cardiff CFS research panel. The healthy controls were partners or friends of the patients, the aim being to control for exposure to infecting agents.

One group of patients and controls completed the diary in the months of October–December (CFS: N = 34; controls: N = 26) and another group in January–March (CFS: N = 28; controls: N = 18). Different viruses may be prevalent at these times so the use of two time periods meant that the replicability of results could be determined. At the end of each week the volunteers completed standard questionnaires relating to the presence of colds and influenza, the nature and severity of symptoms, and their general clinical condition (level of fatigue, general somatic symptoms, mental health).

Measures

The upper respiratory tract illness questionnaire. The first two questions asked whether the volunteer had a cold or influenza that week. If the answer to either of these was 'Yes', the person then recorded the length of illnesses (days) and the presence and severity (0 = not present to 4 = very severe) of the following symptoms: sneezing, runny nose, blocked nose, sore throat, hoarseness, cough, headache, malaise, fever, phlegm, chills, muscle pain and chest pain. Finally, use of medication was recorded.

CFS symptoms. Each week both the patients and controls rated the presence/absence (0 = never to 4 = very often) of physical and mental health problems often reported by CFS patients: physical fatigue, mental fatigue, anxiety, depression, memory problems, concentration problems, indigestion and headache.

Patients and controls
Sixty-two patients were compared with 44 controls. Characteristics of the participants are given in the results section. The Oxford definition of CFS (Sharpe et al., 1991) was used to select patients, all of whom had been assessed previously at the Cardiff CFS clinic.

The Cardiff CFS Clinic
A weekly 'CFS Investigation Clinic' was established in 1992 at the Out-Patients' Department, University Hospital of Wales, supervised by the Section of Infectious Diseases Department of Medicine. Patients come to this clinic from the primary health care setting by standard NHS referral and a full clinical service for patients is provided. Each patient referred to the clinic is examined by the Research Registrar. A full clinical history and examination is performed and recorded on a standardized proforma for later entry into the compiled database. The major features of the disease to be assessed include the nature and duration of fatigue. Particular attention is paid to precipitating factors of disease exacerbation. An objective record of annual visits to the GP is obtained by examination of practice records. Standard clinical/biochemical investigations are performed with specific attention being paid to the exclusion of other physical disease presenting as clinical fatigue. These include: full blood-count and differential blood-count (including film for atypical lymphocytosis),
serum creatinine, urea, electrolytes, liver function tests, C reactive protein (CRP), creatinine phosphokinase, erythrocyte sedimentation rate, urinalysis, immunoglobulins, electrophoresis, thyroid function tests, rheumatoid factor, and DNA antibodies and auto antibody screen. Additional investigations are performed as clinically required. A short, standardized psychiatric interview (SCAN) is undertaken to make an assessment of whether there is overt depression/pyschiatric disease. Following clinical assessment the patients are invited to join the research panel. Participation in research projects is optional to the individual and informed consent is obtained in the usual manner, together with ethical approval for separate projects.

Results

The demographic characteristics of the patients and controls are shown in Table 1. These results show that the groups were well-matched except for gender: there were more females in the CFS group and less females in the control group; because many of the controls were partners of the patients, this was to be expected. However, it also shows that the effect of gender must be considered in subsequent analyses.

Table 1. Demographic characteristics of CFS patients and controls

<table>
<thead>
<tr>
<th></th>
<th>CFS patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>46 Female</td>
<td>19 Female</td>
</tr>
<tr>
<td>Mean age</td>
<td>43.5 years</td>
<td>47.5 years</td>
</tr>
<tr>
<td>Age range</td>
<td>30–70 years</td>
<td>21–71 years</td>
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<tr>
<td>Marital status</td>
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<tr>
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<td>4</td>
</tr>
<tr>
<td>Married</td>
<td>48</td>
<td>38</td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Education level</td>
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<td></td>
</tr>
<tr>
<td>Left school before 16</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Completed secondary education</td>
<td>30</td>
<td>17</td>
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<tr>
<td>University graduate</td>
<td>22</td>
<td>17</td>
</tr>
</tbody>
</table>

The clinical profile of the patients is shown in Table 2. This is very similar to the typical profile seen with this group of patients (see Behan & Bakheit, 1991; Komaroff, 1993; Smith, Behan, Bell, Millar & Bakheit, 1993).

URTIs

Preliminary analyses showed that the partners of the CFS patients did not differ from the other controls. It was deemed appropriate, therefore, to consider them as a single control group. The analyses distinguished the between-participant factors of CFS and controls, study (Autumn vs. Spring) and sex, and the within-participant factor of weeks. The CFS patients reported significantly more colds and influenza than the controls (colds: $F(1,97) = 13.9, p < .005$; influenza: $F(1,97) = 8.0, p < .01$). This effect was apparent in both studies, and male and female volunteers. It was also there for the whole 10-week study period. These results are shown in Table 3.
Table 2. Clinical profile of the CFS patients

<table>
<thead>
<tr>
<th>Duration of illness</th>
<th>Mean (months)</th>
<th>Range (months)</th>
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<tbody>
<tr>
<td>Mean (months)</td>
<td>87.6</td>
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<td>Range (months)</td>
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<th>Time since diagnosis</th>
<th>Mean (months)</th>
<th>Range (months)</th>
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<tr>
<td>Mean (months)</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Range (months)</td>
<td>5–120</td>
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<table>
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<tr>
<th>Current severity (%)</th>
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<tr>
<td>Worse than at any stage</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Bad</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Bad with some recovery</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Recovering with relapses</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Almost recovered</td>
<td>0</td>
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<table>
<thead>
<tr>
<th>Symptoms (%)</th>
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<tr>
<td>Physical weakness (Yes)</td>
<td>79</td>
<td>Sensitive to noise 64</td>
</tr>
<tr>
<td>Excessive fatigue</td>
<td>84</td>
<td>Sensitive to light 58</td>
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<tr>
<td>Legs feeling heavy</td>
<td>69</td>
<td>Feeling hot/cold 73</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>90</td>
<td>Sweating 47</td>
</tr>
<tr>
<td>Pain in chest</td>
<td>31</td>
<td>Shivering 43</td>
</tr>
<tr>
<td>Painful joints</td>
<td>69</td>
<td>Swollen glands 39</td>
</tr>
<tr>
<td>Nausea</td>
<td>40</td>
<td>Racing heart 36</td>
</tr>
<tr>
<td>Indigestion</td>
<td>42</td>
<td>Insomnia 43</td>
</tr>
<tr>
<td>Bloated stomach</td>
<td>43</td>
<td>Depression 36</td>
</tr>
<tr>
<td>Wind</td>
<td>52</td>
<td>Anxiety 40</td>
</tr>
<tr>
<td>Sore throat</td>
<td>43</td>
<td>Loss of concentration 90</td>
</tr>
<tr>
<td>Headache</td>
<td>73</td>
<td>Loss of memory 87</td>
</tr>
<tr>
<td>Earache</td>
<td>31</td>
<td>Allergies 21</td>
</tr>
<tr>
<td>Sore eyes</td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Percentage of volunteers reporting colds and influenza illnesses over the 10-week study period

<table>
<thead>
<tr>
<th>Weeks</th>
<th>CFS patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Colds</td>
<td>Influenza</td>
</tr>
<tr>
<td>1</td>
<td>44.4</td>
<td>6.4</td>
</tr>
<tr>
<td>2</td>
<td>42.1</td>
<td>5.7</td>
</tr>
<tr>
<td>3</td>
<td>29.3</td>
<td>9.9</td>
</tr>
<tr>
<td>4</td>
<td>28.2</td>
<td>6.8</td>
</tr>
<tr>
<td>5</td>
<td>37.1</td>
<td>10.6</td>
</tr>
<tr>
<td>6</td>
<td>34.4</td>
<td>10.4</td>
</tr>
<tr>
<td>7</td>
<td>28.2</td>
<td>7.2</td>
</tr>
<tr>
<td>8</td>
<td>27.4</td>
<td>6.9</td>
</tr>
<tr>
<td>9</td>
<td>39.5</td>
<td>4.7</td>
</tr>
<tr>
<td>10</td>
<td>27.5</td>
<td>3.3</td>
</tr>
</tbody>
</table>
The CFS patients also reported that their illnesses were more severe (mean total symptom score CFS = 15.3, SD = 9.7; mean total symptom score controls = 7.2, SD = 7.5; maximum score possible = 52). The patients were also more likely to use medication than were the controls (percentage using medication for URTIs: CFS = 42.8%; controls = 22.0). However, average length of illness did not differ in the two groups. The above results show a very robust difference in the reporting of URTIs by CFS patients and controls. One possible explanation for this result is in terms of negative affectivity: the CFS patients may be more sensitive to symptoms or have a lower criterion for reporting an illness.

Table 4. Mean rating of the frequency of CFS symptoms (SD)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>CFS patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical fatigue***</td>
<td>3.19 (0.63)</td>
<td>1.52 (0.85)</td>
</tr>
<tr>
<td>Mental fatigue***</td>
<td>2.81 (0.79)</td>
<td>1.25 (0.98)</td>
</tr>
<tr>
<td>Anxiety*</td>
<td>1.72 (0.84)</td>
<td>1.25 (0.97)</td>
</tr>
<tr>
<td>Depression**</td>
<td>1.54 (0.85)</td>
<td>0.87 (0.87)</td>
</tr>
<tr>
<td>Memory problems***</td>
<td>2.54 (0.72)</td>
<td>1.12 (0.97)</td>
</tr>
<tr>
<td>Problems concentrating***</td>
<td>2.56 (0.77)</td>
<td>1.03 (0.89)</td>
</tr>
<tr>
<td>Indigestion***</td>
<td>1.53 (1.10)</td>
<td>0.64 (0.75)</td>
</tr>
<tr>
<td>Headache***</td>
<td>2.07 (0.99)</td>
<td>0.95 (0.83)</td>
</tr>
<tr>
<td>Feeling hot/cold***</td>
<td>1.67 (0.95)</td>
<td>0.61 (0.73)</td>
</tr>
<tr>
<td>Sensitivity to noise or bright light***</td>
<td>1.80 (0.95)</td>
<td>0.52 (0.65)</td>
</tr>
<tr>
<td>Swollen glands***</td>
<td>1.73 (1.03)</td>
<td>0.48 (0.49)</td>
</tr>
</tbody>
</table>

Note. 0 = never to 4 = very often.  
*p < .05; **p < .01; ***p < .001.

Relationship between URTIs and CFS symptoms

One of the aims of the study was to determine whether URTIs influenced the longer term clinical profile of CFS. This was examined in several ways. First, correlations between number of URTIs and change in CFS symptoms over the 10-week period were examined. Second, the volunteers were subdivided on the basis of a median split into those who reported few URTIs and those who reported more. The changes in CFS symptoms of these two groups over the 10-week period were then compared (Table 5). Both methods of analysis revealed that none of the CFS symptom changes were significantly related to frequency of URTIs.

The second set of analyses examined whether having a cold led to a subsequent change in the severity of CFS symptoms. This was done by looking at changes in these symptoms for the week following the cold (those with a cold on this subsequent week were excluded.
from the analyses so that the acute effects of URTIs were not confounded with possible after-effects of the illnesses). Very few of these analyses revealed evidence of a change in CFS as a function of having had an URTI the previous week.

**Discussion**

The present results show that CFS patients report more URTIs, more severe symptoms and greater use of medication for these illnesses than do healthy controls. These findings appear to be robust in that they were observed in male and female volunteers, were not dependent on the season and did not vary over the 10-week period. The next issue to be considered is whether the results reflect increased susceptibility to infection or differences in symptom reporting. There are a number of pathways through which increased susceptibility to infection and illness could occur (see Cohen & Williamson, 1991). As mentioned in the introduction to this paper, CFS patients have, in some studies, been shown to have abnormal immune system functioning. In addition, neuroendocrine abnormalities have been demonstrated and these could be important in the development of infectious diseases. Many CFS patients also abstain from alcohol and this has been shown to be related to an increased incidence of colds (Cohen et al., 1993). It is quite plausible, therefore, that CFS patients are more susceptible to acute infections and this now needs to be examined using appropriate virological techniques. Alternatively, the increased reporting of URTIs could reflect variations in sensitivity to physical sensations, labelling sensations as symptoms, and labelling symptoms as an illness. Indeed, the greater severity of symptoms and increased use of medication fits well with such a schema. It is important, therefore, to use objective measures of symptom severity to determine whether these differ between patients and controls, for if this is the case it is difficult to explain such effects in terms of biases in sensitivity to sensations or in the reporting of symptoms.

**Table 5.** Difference in the rating of symptoms at the end and start of the study by CFS patients who reported less than two URTIs and those who reported two or more URTIs during the 10-week period

<table>
<thead>
<tr>
<th></th>
<th>CFS patients</th>
<th>CFS patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; two URTIs</td>
<td>two or more URTIs</td>
</tr>
<tr>
<td>Physical fatigue</td>
<td>-0.07 (0.73)</td>
<td>0.27 (0.78)</td>
</tr>
<tr>
<td>Mental fatigue</td>
<td>-0.04 (0.94)</td>
<td>0.37 (0.89)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>-0.04 (1.02)</td>
<td>0.00 (0.98)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.44 (1.22)</td>
<td>0.00 (0.91)</td>
</tr>
<tr>
<td>Memory problems</td>
<td>-0.15 (1.15)</td>
<td>0.03 (0.81)</td>
</tr>
<tr>
<td>Problems concentrating</td>
<td>0.22 (0.85)</td>
<td>0.00 (0.87)</td>
</tr>
<tr>
<td>Indigestion</td>
<td>0.19 (1.33)</td>
<td>0.10 (0.92)</td>
</tr>
<tr>
<td>Headache</td>
<td>-0.14 (1.17)</td>
<td>0.10 (1.42)</td>
</tr>
<tr>
<td>Feeling hot/cold</td>
<td>-0.44 (1.12)</td>
<td>0.20 (1.40)</td>
</tr>
<tr>
<td>Sensitivity to noise or bright light</td>
<td>0.07 (1.07)</td>
<td>-0.03 (0.85)</td>
</tr>
<tr>
<td>Swollen glands</td>
<td>-0.89 (1.65)</td>
<td>-0.07 (1.64)</td>
</tr>
</tbody>
</table>

Note. Scores shown are means (SD); positive scores indicate that symptoms were more frequent at the end of the study.
Overall, the different possible interpretations of the present results illustrate two views of CFS that have been frequently debated. The first view is that CFS is 'all in the mind', and would be represented here by saying that the differences between patients and controls reflect biases in symptom reporting. The second approach to the disease suggests that there is some organic disorder that can potentially be detected using objective means (in this case by showing increased susceptibility to the infecting agent). It is clearly incorrect to have such a dualistic approach to the condition. However, in the present context the two approaches can be operationalized and it is clear that a study looking at levels of infection rather than just symptom reporting can clarify whether one view is correct or whether there is evidence supporting both.

Finally, the study examined whether acute URTIs influence the subsequent clinical state of the patients: in other words, do such infections alter the pathogenesis of CFS? The answer appears to be that they do not, although data from a longer time frame is clearly necessary to give a more definitive answer to this issue.

Acknowledgement

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References


3.3 Paper 3

*Chronic fatigue syndrome and URTI*


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An Investigation into the Cognitive Deficits Associated with Chronic Fatigue Syndrome

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Abstract: This study addresses, among other things, the debate as to whether cognitive deficits do occur with a diagnosis of Chronic Fatigue Syndrome (CFS). Previous studies have indicated a potential mismatch between subjective patient ratings of impairment and clinical assessment. In an attempt to tackle some of the methodological problems faced by previous research in this field, this study recruited a large sample of CFS patients where adequate diagnosis had been made and administered an extensive battery of measures. In doing so this study was able to replicate previous published evidence of clear cognitive impairment in this group and demonstrate also that these deficits occurred independent of psychopathology. The conclusion drawn is that cognitive impairments can be identified if appropriate measures are used. Furthermore, the authors have shown that performance changes in these measures have been used to assess both efficacy of a treatment regime and rates of recovery.

Keywords: Chronic fatigue syndrome, cognitive deficits, healthy controls.

INTRODUCTION

Fatiguing illnesses, in particular Chronic Fatigue Syndrome (CFS), are difficult conditions to accurately diagnose and quantify. The Oxford [1] and Centre for Disease Control (CDC) [2] criteria for CFS define a person suffering from CFS as one who has experienced persistent, debilitating mental and physical fatigue for six months or more, where rest is not restorative and the fatigue state is not due to ongoing exertion. There may also be several co-existing symptoms present at any time, including those of a cognitive or neuropsychiatric nature, and once these are established, cognitive, behavioral, emotional, physiological and social factors are thought to work together to perpetuate it [3]. The clinical features of the illness include reports by patients of impaired cognition and research groups have investigated whether an association between mental fatigue and cognitive functioning occurs [4, 5]. Evidence to suggest the existence of impairments in focused attention, speed of processing and performance accuracy in CFS are supported by data which indicate that as sleep deprived, healthy individuals become more fatigued, cognitive deficits become more pronounced [6].

The deficits associated with physical fatigue experienced by CFS sufferers have also been well documented over the past ten years. Decrements in performance on both simple and choice reaction time measures, for example, were indicted by LaManca et al. in 1998 [7] and studies have since revealed impairments in verbal fluency, memory, motor speed, sustained attention and speed of cognitive processing [8-12]. Others have highlighted deficits in verbal and non-verbal memory tasks occurring in this illness [13, 14].

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Others have, however, questioned whether cognitive impairment does actually occur [15, 16], especially in the light of apparent discrepancies between objective measures of impairment and the subjective measures of cognitive failures reported by sufferers [17]. There is evidence to suggest that patient-rated perceived levels of impairment appear much higher than their performance on objective measures. Wearden and Appleby [18], although acknowledging this, indicated that the lack of conclusive data may more likely be explained by the fact that the tasks chosen to assess cognition were not of sufficient sensitivity to measure the impairments in CFS. They further proposed that the performance impairments reported were only evident in tests of a more complicated nature, such as tasks requiring the completion of two or more elements simultaneously (the dual-task paradigm). A recommendation made in light of this paper suggested that future research should employ measures that reflect the nature of the specific cognitive complaints patients themselves report.

Methodological considerations aside, factors such as sample demographics, intelligence, anxiety and depression are known to affect cognitive performance. The link between reaction time, age and intelligence, for example, has long since been established [19]. Similarly, mood disorders such as depression and anxiety are associated with memory and additional deficits [20-22]. In light of this, Michiels and Cluydt [23] expressed the concern that it may be the demographic nature of the patient sample and the presence of co-morbid psychopathology that were responsible for any cognitive deficits reported and not the illness itself. To illustrate this several instances were highlighted where comparison groups had not been sufficiently matched to the CFS sample and screening for co-morbid anxiety and/or depression were not rigorously applied.

To further complicate this particular area of research, the heterogeneous nature of CFS is well documented [24] dictat-
ing that any study investigating cognitive impairment in this illness would require large numbers of patients. Indeed, our previous studies had been conducted on relatively small patient numbers [25] and, although findings were encouraging, it was acknowledged that larger patient numbers were required for a more accurate profile of impairment to emerge. In addition, the analyses conducted would need to be extended to include, not only the potentially confounding factors that co-exist in the illness (such as age, gender and co-morbid depression), but also mechanisms (such as the impact of stress, daily hassles and life events) which appear to exacerbate and perpetuate the condition.

In view of the on-going debate as to the existence and exact nature of the cognitive deficits associated with CFS the current study addressed each of the conflicting issues raised by: (a) recruiting a large sample of Chronic Fatigue Syndrome sufferers from a specialized out-patient clinic where strict adherence to the CDC criteria was maintained [2]; (b) comparing the patient group to an age-, gender- and educationally-matched healthy control group; (c) administering a wide range of objective and subjective measures developed from previous studies [8, 25]; and (d) identifying possible confounding factors which could account for any deficits observed and incorporate them into the analysis model.

MATERIALS AND METHODS

Ethical approval was granted by the local research ethics committee and informed consent was obtained from all who participated. Data were coded to protect the anonymity of both patient and control groups.

Design

Baseline data collected from the patient group were compared to data from a matched group of healthy controls in a between group design.

Participants

Patients, all of whom had been referred by their GP and were attending an hospital infectious diseases outpatient clinic specifically set up to research CFS, were invited to join a volunteer panel administered by the Health Psychology Research Unit. In order to be recruited to the research panel, a patient had to fulfill the Centre for Disease Control (CDC) criteria [2]. Each patient completed a comprehensive batch of computerized mood and cognitive performance tasks as well as a wide range of questionnaires including illness history, psychopathology (in this case co-morbid anxiety and depression), health and well-being. A healthy control group of 126 participants, consisting of members of the general population, was set up by advertisement in local newspapers. This control group provided appropriately age-, gender- and educational-status-matched comparisons for the Chronic Fatigue Syndrome sample. The testing session for both CFS patients and controls were conducted by psychology researchers with an average duration of forty minutes depending on the needs of each participant.

QUESTIONNAIRES

Demographics and Illness History

The demographic section of the questionnaire, as well as collecting data relating to gender, age, social status and educational background of the participants, required the CFS patients to provide a brief history of their illness including illness length, GP involvement in diagnosis, type of onset, illness severity and illness characteristics [8]. The National Adult Reading Test (NART) [26] was used in this study to measure pre-morbid intelligence in the patient and control groups.

Health-related Behaviors

Two variables, namely the average number of hours slept per night and a score rating ‘feeling rested from sleep’, were used to measure sleep quality in the sample. In addition, activity levels, alcohol and cigarette consumption and eating habits were also assessed, as were the use of prescribed medication and dietary supplements [8].

Symptoms and Illness Severity

Both patients and controls also completed a 28-item symptom check list [27], the total scores from which were also used as a measure of illness severity, as was the Profile of Fatigue Related Symptoms questionnaire (PFRS) [28].

Psychopathology, Mood and Cognition

The specific measures described above were considered in conjunction with subjective ratings of positive and negative affect [29], depression [30] and anxiety [31]. In addition, subjective measures of cognition were measured using the Cognitive Failures Questionnaire (CFQ) [32].

Psychosocial Measures

Measures of perceived stress [33], major life events [34], daily hassles [35] and self esteem [36] were used to investigate psychosocial factors and their influence on this illness.

MOOD AND PERFORMANCE TESTING

A battery of computerized performance tests were used to assess mood, memory, attention and psychomotor function [8]. Responses were registered using a response box connected to a timer card allowing measurement of reaction times to the nearest millisecond.

Mood Scales

Subjective mood was assessed using eighteen computerised visual analogue mood scales. Each of these bipolar scales comprised a pair of adjectives, for instance drowsy -- alert or happy -- sad. Participants were instructed to move the cursor from a central position on the scale to a location anywhere along the horizontal line until the cursor rested at a position which was representative of their current mood state. Three scores were derived using factor analysis from the original eighteen items: alertness, hedonic tone and anxiety.

Free Recall

This task assessed short-term recall. Volunteers were shown a list of 20 words presented at a rate of one every two seconds. At the end of the list the volunteer had two minutes to write down (in any order) as many of the words as possible on the sheet provided. The variables measured were the number of words written down, the number of correct words and the number of incorrect words.
Variable Fore-Period Simple Reaction Time Task (Three Minutes Duration)

In this task a frame of a box was displayed in the centre of the screen and at varying intervals (from 1 to 8 seconds) a target square appeared inside the box (approximately 8 per minute). As soon as the participant detected the square, they were required to press the response key using the forefinger of their dominant hand only. A reaction time was measured for each presentation and a mean reaction time was calculated for each minute of performance on the basis of the number of trials completed per minute. An overall mean reaction time was calculated from the total number of trials completed over the duration of the task.

Repeated Digits Vigilance Task (Three Minutes Duration)

This is a measure of vigilance where ability to detect targets at irregular intervals is assessed. Participants were shown successive presentations of three-digit numbers in the centre of the screen (e.g. 473) at the rate of 100 per minute. Each three-digit number usually differed from the one immediately preceding it, with one out of the three digits being replaced with a different digit (e.g. 463, 563, 562). Occasionally (8 times a minute) the same three-digit number was presented on successive trials. It was these repetitions that the participant needed to detect and respond as quickly as possible by pressing a key on the response box using the forefinger of their dominant hand. For each minute of the task and over the duration of the task measures of total mean reaction time to targets, total of trials correctly detected (hits) and the total number of false alarms were recorded.

Distraction from Irrelevant Stimuli

In addition to the computerised tests, the patients and controls carried out the Stroop colour-word interference task [37] which measured distraction from irrelevant stimuli. The task required the participant to complete two control and two test conditions which involved the identification of four colours; red, blue, green or yellow. Firstly, the subject was asked to read the word control card. This involved reading a series of words (red, blue, yellow or green) aloud from left to right and from top to bottom. Next, the participant completed the word test. Here the test card was covered with examples of the four colour words which were coloured differently to that word (that is, the word blue may be coloured yellow, etc.). The volunteer was instructed to read the words only. The third part of the task involved describing the colours presented on the control card (again, from left to right and from top to bottom). Each colour was represented as a series of dots. Finally, the volunteer was asked to repeat the test card; this time describing the colour of the word and not the word itself. Each section of the task was timed using a stopwatch. The times for the word or colour interference section of the task were calculated by subtracting the control time from the test time.

PROCEDURE

Two separate questionnaire booklets were administered in total; one was completed before visiting the clinic or research centre (including demographic data, illness history and symptom severity, health-related behaviours, psychopathology, psychosocial factors and measures of cognition), and one at the time of testing (administered before the completion of the cognitive function tasks and including measures assessing the level of state anxiety, depression, negative and positive affect and fatigue-related symptoms within the previous week).

Sample Size

Priori power analysis [38] calculated an effect size of 0.98 for the simple reaction time task data from our previous study [25]. It was calculated from these data that a sample size of 24 CFS patients and 24 controls would have 95% chance of detecting an impairment effect at the 5% level of significance.

Data Analysis

The first set of analyses described and compared data from the two groups. Categoric data were analysed using Chi-squared tests and analyses of variance were used for continuous data. Repeated-measures analyses of variance were used to assess the impact of time on task.

Next, analyses of covariance were used to identify possible confounding factors for each of the four performance measures (short-term memory, motor speed, vigilance and cognition). Separate analyses were carried out using a range of factors including demographics, health-related behaviours, symptoms, psychopathology, mood and cognition, and psychosocial factors as covariates. Factors identified as those exerting an independent effect on each performance task were included in the analysis model to assess their role in the overall group effect. In addition, these factors (identified as confounds for each performance task) were used as covariates in subsequent analyses.

The final part of the study investigated whether subjective ratings of cognition and illness severity were linked to objective performance deficits within the CFS group as debated previously [17, 18]. Measures, including cognitive failures, fatigue-related measures and total symptom scores, were used as grouping factors for these analyses.

RESULTS

The Chronic Fatigue Syndrome Patient Sample

The CFS group recruited to this study had a mean illness length of five years and 68% of the patients had received a preliminary diagnosis of CFS by their general practitioner (GP). 84% of the patients believed that a specific event had preceded their illness, the majority of these respondents naming influenza as the event (42%), but some (25%) did acknowledge that stress may have had a causative effect. In over 50% of the cases there was no fixed pattern in terms of symptom severity and time of day. The majority of the patients (41%) rated illness status as ‘bad with some recovery’. When asked if there was anything that improved their symptoms, 69% indicated that rest and 50% that sleep had a beneficial effect. Exercise, walking, shopping, mental effort and stress were highlighted as factors which exacerbate symptoms of the illness.

CHRONIC FATIGUE SYNDROME AND CONTROL GROUP COMPARISONS

Demographic Data

Table 1 describes basic demographic data for the CFS and control groups. The groups were very similar in terms of
3.4 Paper 4

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Table 1. The Demographic Data and Health-Related Measures for the CFS and Control Samples. Scores are the Group Means with s.e.m in Parenthesis, or Expressed as Percentages

<table>
<thead>
<tr>
<th>Demographic Data:</th>
<th>CFS (N=307)</th>
<th>Controls (N=126)</th>
<th>F (or χ²), df, p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male: Female (ratio)</strong></td>
<td>30:70</td>
<td>34:66</td>
<td>n/s</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>42.09 (0.67)</td>
<td>40.88 (1.18)</td>
<td>n/s</td>
</tr>
<tr>
<td><strong>Marital Status Married (%)</strong></td>
<td>64.6</td>
<td>50.8</td>
<td>n/s</td>
</tr>
<tr>
<td><strong>Educational Status: Degree level (%)</strong></td>
<td>17.3</td>
<td>16.7</td>
<td>n/s</td>
</tr>
<tr>
<td><strong>Employment Status: Employed (%)</strong></td>
<td>32.4</td>
<td>50.0</td>
<td>24.34, 5, 0.001</td>
</tr>
<tr>
<td><strong>Social Classification: Skilled manual (%)</strong></td>
<td>6.6</td>
<td>13.2</td>
<td>11.69, 5, 0.039</td>
</tr>
<tr>
<td><strong>NART (errors)</strong></td>
<td>14.72 (0.51)</td>
<td>12.48 (0.71)</td>
<td>5.93, 1 430, 0.015</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Health-related Behaviours:</th>
<th>CFS (N=307)</th>
<th>Controls (N=126)</th>
<th>F (or χ²), df, p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication (yes)</strong></td>
<td>61.3</td>
<td>27.0</td>
<td>41.80, 1, 0.001</td>
</tr>
<tr>
<td><strong>Multi-vitamins (yes)</strong></td>
<td>51.0</td>
<td>23.0</td>
<td>28.43, 1, 0.001</td>
</tr>
<tr>
<td><strong>Average Sleep (hours)</strong></td>
<td>7.61 (0.11)</td>
<td>7.30 (0.09)</td>
<td>n/s</td>
</tr>
<tr>
<td><strong>Rested by sleep (never)</strong></td>
<td>18</td>
<td>1</td>
<td>126.00, 4, 0.001</td>
</tr>
<tr>
<td><strong>Eating well (yes)</strong></td>
<td>69.8</td>
<td>65.6</td>
<td>n/s</td>
</tr>
<tr>
<td><strong>Drink alcohol (no)</strong></td>
<td>23.2</td>
<td>9.6</td>
<td>29.81, 3, 0.001</td>
</tr>
<tr>
<td><strong>Smoker (no)</strong></td>
<td>81.8</td>
<td>67.5</td>
<td>10.49, 1, 0.001</td>
</tr>
<tr>
<td><strong>Exercise (never)</strong></td>
<td>47.4</td>
<td>19.7</td>
<td>52.68, 1, 0.001</td>
</tr>
</tbody>
</table>

age, gender and educational status. There were no significant differences between the two groups in terms of marital status or social classification.

These data, however, indicate that the CFS group were significantly less likely to be in employment than the controls at the time of testing.

Although, as stated above, the two groups were matched in terms of educational status, the CFS group made significantly more errors on the pre-morbid intelligence test than the controls (see Table 1).

Health-related Behaviours

Although there was no significant difference between the average number of hours slept by the two groups, the CFS group was significantly less likely to feel rested from sleep (see Table 1). The CFS group were significantly more likely to be taking prescribed medication and dietary supplements than the control group. The controls were also significantly more likely to smoke and consume alcohol than the patient group and were more likely to exercise regularly. There were no differences between the two groups in terms of food intake.

Symptoms and Illness Severity

When considering the symptom check-list, there were statistically significant differences between the CFS and control groups on each of the 28 items on the scale (p<0.001) and, therefore, the mean total symptom scores for the CFS patients was significantly higher than the control group. As one might expect in this group of patients, the CFS group recorded higher fatigue ratings on the Profile of Fatigue Related Symptoms scale [28]. On this scale they also recorded significantly higher levels of emotional distress, cognitive difficulties and somatic symptoms (see Table 2).

Psychopathology, Mood and Cognition

Participants were asked to rate their responses relative to the previous week including the day of testing (see Table 3).

Table 2. Symptom and Illness Severity Scores (from the PFSS Scale) for the CFS and Control Sample. Scores are the Group Means with s.e.m in Parenthesis. Higher Scores=Greater Symptom/Illness Severity

<table>
<thead>
<tr>
<th>Symptoms:</th>
<th>CFS (N=307)</th>
<th>Controls (N=126)</th>
<th>F, df, p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Symptoms (n=28)</strong></td>
<td>15.76 (0.32)</td>
<td>2.69 (0.28)</td>
<td>618.90, 1 426, 0.001</td>
</tr>
<tr>
<td><strong>Fatigue Related Symptoms:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED</td>
<td>47.80 (1.21)</td>
<td>32.51 (1.40)</td>
<td>53.56, 1 426, 0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>62.90 (0.89)</td>
<td>23.05 (1.04)</td>
<td>679.10, 1 424, 0.001</td>
</tr>
<tr>
<td>CD</td>
<td>46.89 (0.92)</td>
<td>23.58 (0.94)</td>
<td>226.50, 1 426, 0.001</td>
</tr>
<tr>
<td>SS</td>
<td>53.27 (1.13)</td>
<td>23.51 (0.78)</td>
<td>269.20, 1 424, 0.001</td>
</tr>
</tbody>
</table>

ED = Emotional Distress; CD = Cognitive Difficulties; SS = Somatic Symptoms.
These data suggest that the CFS patients were more depressed than the controls. In response to the more generalised questions posed in the pre-visit booklet, the trait anxiety scores for the CFS patients were significantly higher than those of the controls as were the levels of cognitive failures. However, there was no significant difference between the two groups in terms of anxiety (CFS=40.42, controls=41.67; p=0.20) when the participant was asked to rate how they felt on the day of testing. The CFS group did report lower positive and higher negative mood scores than the controls during the previous week. These mood data also showed that the CFS group were significantly less alert than the controls, had lower hedonic tone scores and were more anxious than the control group (see Table 3).

Psychosocial Measures

The CFS group reported significantly higher levels of perceived stress, suffered more severe daily hassles and less positive life events than the controls. However, there were no significant differences between the groups in terms of self-esteem or negative life events (see Table 4).

**Performance Testing**

Data comparing the CFS and controls in terms of performance measures are depicted graphically in Fig. (1).

**Free Recall**

The CFS patients recalled significantly fewer words than the healthy controls indicating deficits in episodic memory in the patient group (CFS=6.12 words, controls=7.48 words; F(1,430)=39.92, p<0.001).  

**Simple Reaction Time Task**

The mean reaction time (mRT) over the 3 minutes of the test was significantly longer for the CFS patients than the controls (CFS=490.81 msec, controls=284.15 msec; F(1,430)=34.30, p<0.001).
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An Investigation into the Cognitive Deficits Associated with CFS

Data describing the time-on-task reaction times over the 3 minutes (that is the RT for each minute of the task) suggests that there is a linear group effect for reaction times (F(1,429)=67.20, p<0.001) indicating that both groups' reaction times slow gradually over the three minutes. CFS patients had slower reaction times on each minute of the task (time on task), and the repeated measures analysis indicated that the CFS groups' reaction time slowed at a greater rate (F(1,858)=3.03, p<0.05) than the controls (i.e. they become fatigued more quickly than the controls – see Fig. 2).

Repeated Digits Vigilance Task

Again the overall mean reaction time for the CFS patients on this task was significantly slower than the controls (CFS=611.7msec, controls=549.4msec; F(1,383)=26.80, p<0.001). There was no time-on-task effect in the vigilance task even though group differences in the reaction times for each minute on the task remain. The total number of correctly detected targets (hits) was also significantly lower in the CFS group (CFS=11.12 hits, control=13.75 hits; F(1,423)=34.30, p<0.001) but there no overall time-on-task group effect. The control group detected significantly fewer hits in minute 2 when compared to minute 1 (min 1=5.31, min 2=4.94; F(2,124)=59.33, p<0.01) and significantly fewer hits in minute 3 compared to minute 2 (min 2=4.94, min 3=3.50; F(2,124)=59.33, p<0.001). However, although the CFS group detected significantly fewer hits in minute 3 than minute 2 (min 2=4.24, min 3=2.81; F(2,296)=86.21, p<0.001) there was no difference between the number of hits detected between minutes 1 and 2.

There was no difference between the two groups in terms of false alarms.

Distraction from Irrelevant Stimuli

Analysis of covariance on the Stroop test, with the word control condition as a covariate, produced no significant differences between the groups when measuring colour interference (name the word, ignore the colour). The CFS group, however, were significantly slower than the controls when naming the colour and ignoring the word (CFS=113.52 seconds, controls=85.91 seconds; F(1,427)=52.68, p<0.001).

IMPAIRED COGNITION AND POSSIBLE CONFOUNDING FACTORS

As factors such as demographics, symptoms, anxiety, depression, mood and psychosocial factors have been shown...


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Table 5. Confounding Factors which are Known to Exert an Independent Effect on Cognition. Factors Ultimately Identified in the Analyses are Highlighted in Bold

<table>
<thead>
<tr>
<th>Stroop</th>
<th>Free Recall</th>
<th>Simple Reaction Time</th>
<th>Repeated Digits Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>Word interference</td>
<td>Words recalled</td>
<td>Mean reaction time</td>
<td>Digits detected</td>
</tr>
<tr>
<td>Gender</td>
<td>Age</td>
<td>Marital Status</td>
<td>Gender</td>
</tr>
<tr>
<td>Educational Status</td>
<td>Age</td>
<td>Educational Status</td>
<td>Educational Status</td>
</tr>
<tr>
<td>Employment Status</td>
<td>Employment Status</td>
<td>Social Classification</td>
<td>Employment Status</td>
</tr>
<tr>
<td>NART</td>
<td>Social Classification</td>
<td>NART</td>
<td>Social Classification</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Free Recall</th>
<th>Simple Reaction Time</th>
<th>Repeated Digits Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reasted by sleep</td>
<td>Stroop</td>
<td>Medication</td>
<td>Rested by sleep</td>
</tr>
<tr>
<td>Emotional Distress</td>
<td>Emotional Distress</td>
<td>Emotional Distress</td>
<td>Emotional Distress</td>
</tr>
<tr>
<td>Cognitive Difficulties</td>
<td>Cognitive Difficulties</td>
<td>Cognitive Difficulties</td>
<td>Cognitive Difficulties</td>
</tr>
<tr>
<td>Somatic Symptoms</td>
<td>Somatic Symptoms</td>
<td>Somatic Symptoms</td>
<td>Somatic Symptoms</td>
</tr>
<tr>
<td>Physical Symptoms</td>
<td>Physical Symptoms</td>
<td>Physical Symptoms</td>
<td>Physical Symptoms</td>
</tr>
<tr>
<td>Depression</td>
<td>Depression</td>
<td>Depression</td>
<td>Depression</td>
</tr>
<tr>
<td>Trait Anxiety</td>
<td>Trait Anxiety</td>
<td>Trait Anxiety</td>
<td>Trait Anxiety</td>
</tr>
<tr>
<td>Positive Mood</td>
<td>Positive Mood</td>
<td>Positive Mood</td>
<td>Positive Mood</td>
</tr>
<tr>
<td>Negative Mood</td>
<td>Negative Mood</td>
<td>Negative Mood</td>
<td>Negative Mood</td>
</tr>
<tr>
<td>Cognitive Failures</td>
<td>Cognitive Failures</td>
<td>Cognitive Failures</td>
<td>Cognitive Failures</td>
</tr>
<tr>
<td>Daily Hassles</td>
<td>Daily Hassles</td>
<td>Daily Hassles</td>
<td>Daily Hassles</td>
</tr>
<tr>
<td>Perceived Stress</td>
<td>Perceived Stress</td>
<td>Perceived Stress</td>
<td>Perceived Stress</td>
</tr>
</tbody>
</table>

SUBJECTIVE MEASURES OF COGNITION VERSUS OBJECTIVE MEASURES OF PERFORMANCE

The Cognitive Failures Questionnaire (CFQ) was used in this study as a subjective measure of cognitive impairment. To investigate the suggestion that patients with CFS overestimate the levels of cognitive deficits experienced, a median split was performed on the CFQ scores for each of the two groups and, as a result, four sub-groups were created: (a) CFS patients with low CFQ scores (n=107), (b) controls with low CFQ scores (n=106), (c) CFS patients with high CFQ scores (n=186) and, (d) controls with high CFQ scores (n=16). These were then used as grouping factors in analyses of variance for each of the performance measures with the independent factors highlighted in Table 5 as covariates. These results are shown in Table 6.

Table 6. Subjective Measures of Cognition (Cognitive Failures) Versus Objective Measures of Performance. Scores are the Group Means with s.e.m in Parenthesis. Higher Stroop and RT Scores=Slower Reaction Times

<table>
<thead>
<tr>
<th>Low CFQ:</th>
<th>Stroop (sec.)</th>
<th>Free Recall</th>
<th>Simple Reaction Time (msec.)</th>
<th>Repeated Digits Task (detected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFS</td>
<td>101.69 (3.14)</td>
<td>6.26 (0.20)</td>
<td>400.70 (21.73)</td>
<td>11.77 (0.40)</td>
</tr>
<tr>
<td>Controls</td>
<td>88.48 (3.16)</td>
<td>6.79 (0.23)</td>
<td>320.27 (22.26)</td>
<td>12.68 (0.43)</td>
</tr>
<tr>
<td>High CFQ:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFS</td>
<td>117.95 (2.40)</td>
<td>6.44 (0.19)</td>
<td>523.25 (16.91)</td>
<td>14.64 (1.00)</td>
</tr>
<tr>
<td>Controls</td>
<td>89.14 (8.12)</td>
<td>7.41 (0.45)</td>
<td>282.68 (55.02)</td>
<td></td>
</tr>
<tr>
<td>Group Effect:</td>
<td></td>
<td></td>
<td></td>
<td>F(3,409)=19.94, p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F(3,409)=2.93, p=0.033</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F(3,406)=19.398, p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F(3,403)=4.15, p&lt;0.006</td>
</tr>
</tbody>
</table>

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There is an overall group effect of CFQ on cognition and, therefore, an association between the subjective CFQ measure and level of cognitive deficit in CFS.

To further investigate the relationship between subjective and objective measures, the cognitive failures questionnaire scores for the patient and control groups were split into their respective quartiles and used as grouping factors.

These analyses reveal clear differences between the CFQ quartiles for both the mean reaction time task (F(3, 285)=3.32, p<0.02) and the Stroop task (F(3, 287)=4.78, p<0.003), but not for the free recall or vigilance tasks. For the controls, however, there were no associations between CFQ scores and deficits for any of the performance measures.

**Illness Severity and Performance**

Two measures, namely the total symptom scores and the Profile of Fatigue Related Symptoms (PRFS), were used to assess illness severity in the patient sample. To investigate the relationship between illness severity and cognitive deficits, these two measures were dichotomised and summed to create six groups (a) low illness severity CFS patients (n=61), (b) low illness severity controls (n=117), (c) medium illness severity CFS (n=57), (d) medium illness severity controls (n=8), (e) high illness severity CFS (n=175) and, (f) high illness severity controls. Unfortunately, there were no controls in the high illness severity grouping and only eight in the medium illness severity control group. Data for the medium illness severity controls have been included in Table 7 (which describes these data for each performance task) for comparison purposes but will not be discussed further.

There was an overall group effect for free recall scores, with there being significant differences between the low illness severity controls and the medium and high illness severity patients (p<0.001 and p<0.002 respectively). However, there were no indications of an association between illness severity and performance deficits in the CFS groups.

There was also an overall group effect in the simple reaction time task, with there being significant differences between the low illness severity controls and the low, medium and high illness severity patients (p<0.04, p<0.001 and p<0.001 respectively). In addition, there were significant differences in the time taken to complete the task by the low and high illness severity patients (p<0.001) and the medium and high illness severity patients (p<0.001). However, there was no significant difference between the low and medium illness severity patients.

These data provide a similar profile to that of cognitive failures: that is, there were associations between the level of illness severity and cognition for the two reaction time tasks but not for the recall and vigilance tasks.

**DISCUSSION**

The current study set out to bring some clarity to the issues arising from the on-going debate surrounding the exact nature, and indeed existence, of the cognitive deficits associated with Chronic Fatigue Syndrome (CFS). This was achieved by addressing specific comments made by previous reviewers of the literature [17, 18] as well incorporating into the design the views of those who found no evidence of such impairment [7, 15, 16].

To begin with we recruited 307 participants, a much larger number of patients than previous studies, from a single specialised outpatient clinic. To address the issue of accuracy of diagnosis, the Centre for Disease Control (CDC) case definition criteria [2] was used to diagnose all patients invited to take part in the study, which excludes patients exhibiting major psychiatric disorders. It was clear that our sample conformed to the expected demographic profile for Chronic Fatigue Syndrome (CFS): that is, a predominance of middle-aged married females.

**Table 7. Illness Severity Versus Cognitive Performance. Scores are the Group Means with s.e.m in Parenthesis. Higher Stroop and RT Scores=Slower Reaction Times**

<table>
<thead>
<tr>
<th>Illness Severity:</th>
<th>Stroop (sec)</th>
<th>Free Recall (words)</th>
<th>Simple Reaction Time (msec)</th>
<th>Repeated Digits Task (digits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low severity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFS</td>
<td>98.32 (4.04)</td>
<td>6.70 (0.24)</td>
<td>387.23 (29.07)</td>
<td>11.98 (0.51)</td>
</tr>
<tr>
<td>Controls</td>
<td>88.31 (2.94)</td>
<td>7.04 (0.20)</td>
<td>315.00 (21.35)</td>
<td>13.11 (0.41)</td>
</tr>
<tr>
<td>Medium severity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFS</td>
<td>99.185 (4.18)</td>
<td>6.23 (0.24)</td>
<td>466.73 (29.33)</td>
<td>11.38 (0.54)</td>
</tr>
<tr>
<td>Controls</td>
<td>92.07 (11.25)</td>
<td>6.87 (0.63)</td>
<td>325.41 (78.21)</td>
<td>12.52 (1.41)</td>
</tr>
<tr>
<td>High severity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFS</td>
<td>120.62 (2.40)</td>
<td>6.21 (0.16)</td>
<td>516.30 (17.72)</td>
<td>11.21 (0.33)</td>
</tr>
<tr>
<td>Group Effects:</td>
<td>F(4,41)=19.78, p&lt;0.000</td>
<td>F(4,404)=2.64, p&lt;0.034</td>
<td>F(4,404)=13.32, p&lt;0.000</td>
<td>F(4,405)=2.94, p&lt;0.020</td>
</tr>
</tbody>
</table>

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When examining the patient sample in more detail we found that the majority of the group (68%) had received a preliminary diagnosis of CFS from their GP before attending the clinic and their mean illness length was five years. Although the majority of patients suggested a physical cause as a possible trigger for their illness (such as influenza), several patients acknowledged a non-physical cause (for example, a stress-related episode).

Half the sample of patients experienced fluctuations in symptom severity although no regular daily pattern emerged. The resultant effect of such variability is that patients experience high levels of uncertainty. Data from a symptom check list provided evidence of the myriad symptoms experienced by CFS sufferers. The study showed that and the majority of patients (41%) reported their condition as ‘bad with some recovery’ on the 5-item current state of health scale at the time of testing. Increased rest and sleep were highlighted by patients as the most effective approaches in their attempt to minimise the negative effects of the illness whilst, on the other hand, exercise, walking, shopping, mental effort and stress were most commonly linked with an exacerbation of symptom severity.

To address criticisms aimed at the inclusion of inappropriate control groups in previously reported studies, we recruited 126 healthy volunteers from a cross-section of the general population who were matched to the patient sample in terms of age, gender, educational standard and socio-economic group. In addition, the controls completed a similar screening process to the patient group.

Concerns voiced by Wearden and Appleby [18] regarding the suitability and sensitivity of the objective measures of cognitive performance used in previous research were answered by administering tasks which, not only reflected the type of cognitive impairments patients themselves report, but the tests used had been utilised in previous studies of the illness [8, 25] and in studies of fatigue in healthy individuals [6].

In a series of group comparisons we found several differences between the CFS patients and control group. Firstly, and not surprisingly considering the severity of the illness, the controls were significantly more likely to be in employment than the CFS group at the time of testing. Secondly, despite the two groups being matched in terms of educational status, the CFS patients scored significantly lower on the pre-morbid intelligence measure than the controls. There are two possible explanations for this: (a) intelligence shows a positive correlation with most cognitive measures [39], the converse is also true, namely that deficits in cognitive functioning will be accompanied by lower intelligence scores; (b) patients with depression have been shown to report lower pre-morbid intelligence scores using the NART score [40].

A further area of interest is the role of sleep abnormalities in this illness [8]. Our data suggests that the average number of hours slept per night did not differ between the patient and control groups. However, the two groups were shown to differ in ratings of the extent to which the individual felt rested as a result of sleep – namely sleep quality. Abnormalities in sleep patterns had been shown to affect mood and performance both in CFS patients and healthy controls [8, 27] and were an important factor to consider when examining these data further. In addition, problems with sleep quality are often observed in abnormal psychopathology [41, 42].

The presence of co-morbid mood disorder is also indicated in the patient group. Although these findings contradict previous findings (e.g. Marshall et al. 1996 [14]), it is believed that this study provides a more accurate representation of the illness due to the fact that a larger cohort was assessed in comparison with previous studies. Indeed laboratory testing further highlights the differences between the mood states of the two groups. The CFS patients record significantly lower levels of irritability and hedonic tone and have higher anxiety levels than the control group. It is of note that the state anxiety scores of the two participant groups do not differ at the time of testing, indicating that the patient group was not unduly distressed by the test session itself. Trait anxiety scores, however, indicate that patient group exhibit higher general anxiety levels than the controls.

Simple comparisons of performance task data seem to confirm our previous findings of a slowing of motor speed and impairments in immediate recall in CFS. The reaction time task also provides data indicating that there were significant differences between the reaction times of the CFS and control groups when comparing reaction times at minute intervals. In addition, a greater rate of slowing over the three minutes was seen in the CFS group. This ‘time-on-task effect’ was not replicated in the other three minute task (the vigilance task) even though group differences in the reaction times for each minute on the task remain. There is a suggestion here that although both sustained attention and motor speed are affected in CFS, time-on-task effects differ. A possible explanation may be that performance on such tasks are affected differently by fatigue and that these differences may reflect differences in underlying neurotransmitter mechanisms involved in processing the two tasks (Christopher et al. 2005 for a discussion [43]). However, this theory would have to be tested in further wide-ranging studies.

Returning to the vigilance task, the detection rate of repeated digits for each minute was greater in the control group than the patient group and both groups’ detection rate decreased over time. In contrast to our previous findings, where a gradual decline in accuracy over time was reported for both groups [25], the current study indicates that there was no measurable decline in accuracy for the patient group between minutes 1 and 2. A trade-off between reaction time and accuracy (for minutes 1 and 2) is, however, observed in healthy controls and this warrants further investigation.

The final performance task, the Stroop interference task [37], provided evidence to suggest that distraction by irrelevant stimuli is more pronounced in the patient group. These data are contrary to findings reported by Metzger and Denny [44] who found no evidence to suggest that CFS patients perform differently to controls on this task. The inconsistency between their study and the results presented here might be due to the relatively small number of patients tested (40 compare to 307) and the fact that a modified version of the Stroop task was used to assess cognitive function. By modifying the task, some test sensitivity may have been lost and this has been suggested as a possible reason for the lack of conclusive data in the past.
To investigate these data further, a series of additional analyses were conducted, this time identifying a range of factors significantly associated with poorer performance and including these as covariates in the analyses. These included demographic data, pre-morbid intelligence, illness severity, anxiety, depression, psychosocial factors and sleep data. Only two variables, total symptoms and the fatigue sub-scale of the fatigue-related symptoms questionnaire, were identified as factors which act to remove the overall group effect on performance. Although one might expect the level of somatic symptoms, cognitive difficulties and emotional distress to be major factors of influence in this particular illness, these two factors essentially define the two groups. However, several factors were identified as having an independent effect on performance without removing the overall group effect. These factors were, therefore, used as covariates in further analyses to ensure that they could act in cumulative way and affect performance. There was no evidence to suggest that co-morbid anxiety and/or depression play a role in the level of cognitive deficit in this illness.

In order to consider the ability of the patient group to subjectively assess their level of cognitive impairment accurately, data from the Cognitive Failures Questionnaire (CFQ) were used [32]. Previous studies showed that the subjective ratings of cognitive deficits by CFS patients were much higher than the level of deficits identified on objective measures of performance. Patients recording high scores on the Cognitive Failures Questionnaire performed significantly worse than those recording low scores for the two reaction time tasks. These data indicate that patients are more able to accurately subjectively rate their cognitive performance than previous reports have indicated [18].

It was also important to investigate whether illness severity negatively affects cognitive functioning, that is are the more severe cases of CFS more functionally impaired. Illness severity as weighted by splitting the patients according to their fatigue-related symptoms and total symptom scores. These scores were then summed and compared to each performance task allowing us to look at performance across a range of severity scores. The controls performed better on each of the tasks than the patient groups even those rated with low illness severity. When considering the CFS group alone, an association between illness severity and poorer cognitive performance is seen in the psychomotor tasks but not the accuracy or recall tasks. These outcomes are partly in agreement with previous studies [17, 18] but also raises further questions as to the exact nature of the cognitive impairment associated with CFS.

Recruiting patients via a specialised out-patients raises issues about generalisability and this is acknowledged as a limitation of the study. However, our data indicating a measurable deficit in motor speed are in keeping with findings from a recent population-based study [45].

CONCLUSION

The current study provides compelling evidence, not only for the existence of cognitive deficits in Chronic Fatigue Syndrome, but for the nature of these same impairments. Of interest here is that these objectively measured deficits remain even when factors associated with performance impairments are taken into consideration. Improvements or recovery from the illness should, therefore, be accompanied by improvements in cognition. The possibility of measuring recovery in these terms is indicated here: indeed, recent research provides evidence that some of the performance measures used in this study may be valid indicators of recovery [46]. Further studies are, however, required to investigate the possible mechanisms underlying our findings. One area of interest may be the influence of specific neurotransmitters such as acetylcholine, noradrenaline and dopamine in cognitive functioning. Another is the role of insulin in modulating acetylcholine and noradrenaline which in turn influences cognitive functioning. Similarly, dopamine has also been shown to influence motor functioning, verbal fluency, episodic memory and executive functioning [47, 48]. In addition, several groups have identified neuro-anatomical abnormalities in patients with CFS using neuroimaging techniques. These include reduced regional cerebral blood flow, anatomical abnormalities in cortical and subcortical regions and reduced glucose metabolism. The impact of such abnormalities are likely to impact on cognitive performance and may go some way in offering an explanation for some of the cognitive impairments observed in the current study.

There remains a large gap in the current body of scientific knowledge as to the nature of these abnormalities. One area of interest is ‘cause and effect’: that is, do the abnormalities observed cause CFS or does the decrease in physical activity resulting from the illness produce the abnormality. For example, there have been reports of a link between physical activity and neurogenesis [49]. In addition, recent studies have also suggested that neurogenesis is involved in the action of antidepressants [50]. These findings may explain the increased recovery rates detected in CFS patients prescribed antidepressant medication in our study [51].

Finally, there is an emerging hypothesis based on the model of "altered self" which refers to the immune response to infection [52]. Infectious diseases are often accompanied or followed by periods of fatigue, disturbed sleep and an inability to concentrate. The theory is widened to a brain function model where an extended concept of altered self means that the patient does not return to the non-disease state due to the brains failure to recognise that state [52].

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REFERENCES

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Measuring Recovery in Chronic Fatigue Syndrome Patients and Assessing the Impact of Associated Risk Factors on Positive Outcome
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ABSTRACT

Background: The current study describes a large cohort of untreated Chronic Fatigue Syndrome patients at initial assessment and examines changes within the illness over three years. Furthermore, a ‘current state of health’ scale, developed in previous studies, was validated for use as a method for accurately measuring recovery. Possible predictors of outcome were then identified by investigating the role of baseline measures in subsequent recovery.

Methods: 226 patients completed questionnaires at initial assessment. The current state of health score was used to measure recovery six, eighteen months and three-years later. Associations between baseline measures of fatigue, psychopathology, mood, cognition, stress and current state of health were examined to look at the validity of the state of health measure. Demographic and psychosocial characteristics were investigated as predictors of recovery. Illness characteristics such as illness length, illness onset type and illness beliefs were also investigated as predictors of outcome.

Results: There was strong evidence to suggest that the current state of health measure accurately describes the patient’s health at baseline. Spontaneous recovery rates in the untreated patient at three year follow-up were low at only 6%. These data suggested, however, that illness length, symptom severity and health status have an important role in recovery. There was no evidence of an association between illness onset type and subsequent recovery or psychopathology scores at initial assessment and recovery.

Conclusions: The current state of health measure was validated as a method of accurately assessing the health status of patients and was used as an indicator of improvement and recovery within this group. Spontaneous recovery in the patient group was associated with several factors measured at initial assessment. However, further studies are necessary to more fully identify the factors which affect recovery and to investigate the exact nature of the mechanisms involved.
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BACKGROUND
The fatigue experienced in Chronic Fatigue Syndrome (CFS) is not only of sufficient severity to cause substantial functional impairment, but is accompanied by four or more co-existing symptoms including those of a cognitive or neuropsychiatric nature (Centre for Disease Control (CDC) criteria) [1]. The illness (by definition) must be of at least six months duration and can become very debilitating and persistent [2]. Although the incidence of CFS in the general population is relatively low [3-5], this should not detract from the severe effect the illness has on the individual sufferer’s quality of life. Decreased personal, occupational and social activities combine to instil a sense of frustration and hopelessness within the patient. In addition, financial concerns have been raised regarding the increased uptake of unemployment benefits and the drain on healthcare resources caused by the illness. Data collected as part of the CDC’s surveillance study estimated that the cost in terms of lost productivity, per annum, for each CFS patient in the United States was $20,000 [6]. In the light of this, continued research into the causes of and potential therapies for CFS is vital if this financial burden was to be alleviated [7].

Before coherent treatment protocols were in place research mainly concentrated on investigations into the long-term prognosis of CFS. These longitudinal studies also attempted to calculate recovery rates and identify possible predictors of positive outcome (or recovery). Predictions of recovery rates in the untreated illness have, however, produced spurious results. A review of the literature indicated that such discrepancies in the research could be explained by the use of several different criteria to define recovery in the patient group. For example, a patient in recovery (or remission) was described in one study as; (a) no longer suffering from fatigue, (b) experiencing less than four CFS related symptoms and, (c) a person whose health no longer interfered with normal activities [6]. When these criteria were applied, spontaneous recovery was calculated at 31.4% during the first five years of the illness. On the other hand, an assessment of 98 consecutive referrals to a specialised CFS clinic produced data suggesting that although 41% of the sample were moderately to completely recovered two to three years post-baseline, only 2.6% of these patients rated themselves as ‘fully recovered’. However, 29.5% of the patient sample felt well enough to have returned to work during this time [8]. A discussion by Cairns and Hotopf highlighted inconsistencies in the literature and concluded that although improvement in patients at follow-up ranged from 8 to 63%, full recovery from the illness was actually quite rare [9].

The inconsistencies outlined above may be due to the fact that measuring recovery in the particular case of CFS is confounded by reports from sufferers of periods of remission throughout the illness (typically observed in patients with short illness duration for example) [6, 10]. Ideally therefore, any measure of recovery should be validated by several independent illness-related measures to evaluate its capability to differentiate between true recovery and bouts of remission. In addition, longitudinal studies are, by definition, conducted over several years. One can not presume that, although the studies reviewed were not part of any specific treatment protocols, the patients questioned did not attend some form of therapy during the intervening time period. These data might not, therefore, represent the true nature of the illness and this may be being reflected in high recovery rates. In the current study we, therefore, aimed to validate the accuracy of a measure (developed previously) to represent recovery in the patient group [11]. Factors including younger age at onset, fewer physical symptoms, higher mental and general health scores and low levels of emotional distress at baseline have also been
put forward as possible indicators of recovery in CFS [8]. In addition, low levels of fatigue (at baseline), a sense of control over the symptoms associated with the illness and the attribution of non-physical cause have also been linked with more favourable outcomes [9]. Furthermore, several aspects of the disorder such as psychopathology, ratings of well-being, psychosocial and demographic factors have been implicated in outcome [11]. Previous studies had also indicated that there were possible confounding variables which affect the severity of CFS including psychosocial factors, support mechanisms, health measures, psychopathology and cognition [11, 12].

To investigate aspects of recovery in CFS further the current study aimed to, in the first instance, describe the characteristics of a large cohort of sufferers at initial assessment. The study then aimed to validate a simple measure for accurately measuring the health status of the individual patient and use it to define and assess recovery. In addition, possible predictors of outcome were investigated by comparing the health, psychosocial measures and cognition (at initial assessment) of patients who recovered over a three year period to those who did not recover. These data also allowed us to monitor the natural progression of the untreated illness over time.

**METHODS**

**Design**
The study was longitudinal in nature, with assessments occurring at initial clinic visit (baseline) and six, eighteen months and three years later.

**Participants**
Ethical approval for the study was granted by the local health authority. Potential volunteers were informed that the research was being conducted as part of a long-term project investigating CFS and that they would be asked to complete similar test batteries over a period of time as part of a research panel. Participation in the study was voluntary and written, informed consent obtained. Patient data were coded to ensure anonymity.

The research panel comprised consecutive GP referrals to a specialised CFS outpatient clinic that fitted the CDC criteria for Chronic Fatigue Syndrome [1]. Patient volunteers were assessed at initial clinic visit (baseline), at six and eighteen months and again three years later. As there was no formal treatment available to these patients at that time these data represent the untreated illness. However, a small number of participants were taking antidepressant therapy at baseline. Data for these patients were not included in the final analyses and the findings are reported elsewhere [13].

**Materials and Method**
The CFS volunteers completed a range of questionnaires developed to measure global ratings of well-being, sleep and psychopathology and established indicators of quality of life [11, 12, 14]. Demographic data relating to the sample were collected along with an illness history questionnaire and a 28-item symptom check-list. The resulting data were then used to examine associations between these measures and recovery over time.

**Measurement of Recovery**
Health status and severity were measured by a ‘current state of health measure’ developed previously [11]. This 5-item scale categorised the patients health as follows: (a) worse than at any stage of the illness; (b) bad; (c) bad with some
recovery; (d) recovering with occasional relapses and (e) almost completely recovered.

For the purpose of the current study, in order to compare those patients who recovered over time to those who did not, the current state of health measure was dichotomised into; (a) patients who were in the ‘almost completely recovered’ category (item five on the scale) and (b) those patients categorised by the other four items. Furthermore, the concept of recovery was widened to include patients in the ‘recovering with occasional relapses’ category. In this way, if predictions of low spontaneous recovery rates reported previously were proven [9], this broader indicator of recovery would be used in any further analyses.

Procedures
The individual questionnaire measures were packaged in the form of two booklets; (a) demographics, illness history/symptoms and general illness traits [11, 15, 16], (b) illness symptoms experienced in the previous week [11, 17-20]. Patients were asked to complete the questionnaire booklets at home and at their own pace to minimise questionnaire fatigue. The booklets were returned to the research unit in pre-paid envelopes.

Patients also responded verbally to a range of questions relating to illness beliefs including type of onset (acute or gradual) and events which were thought to have preceded the illness. These data were recorded by research registrars at initial clinic visit.

To measure recovery over time, the current state of health variable was administered at initial clinic visit (baseline) and six, eighteen and thirty-six months later. The three-year follow-up questionnaires had a return to sender advice to assess how many of the panel had moved during the evaluation period.

Data Analysis
Initial analyses were carried out to determine the characteristics of the sample at baseline. Analyses of variance were used for continuous data and categoric data from the study were analysed using Chi-squared cross-tabulation. These methods of analyses were also used to test the comparability between the baseline demographic and illness history data of the original CFS cohort to those completing the three-year session.

In order to test the validity of the current state of health to accurately describe health status at any given time, it was compared to other health-related measures known to be associated with the illness such as, mood, symptoms and psychosocial factors. To achieve this, the continuous measures were split into quartiles and subjected to Chi-squared cross-tabulation analyses with items from the current state of health measure. To test the validity of the current state of health variable to measure recovery, patients were categorised into two groups at baseline: those who were not recovering and those who thought they were recovering. Independent sample t-tests were then carried out to validate this measure by investigating the relationship between the current state of health variable and other health measures and psychosocial factors at baseline.

Once validated, predictors of outcome were identified by independent sample t-test analyses with recovery at three-year follow-up used as grouping variable. To investigate these relationships further, continuous variables were split into quartiles and cross-tabulated with the recovery variable.
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RESULTS
In all, 307 CFS patients were recruited to the research panel. Patients taking antidepressant medication at baseline and for those whom antidepressant medication status was unknown (n=81) were excluded from the final analyses. 130 patients completed all assessment time points and 40 participant questionnaires were returned to sender.

Baseline Patient Sample and Illness Characteristics
Table 1 describes the basic demographic data for the 226 patients at baseline. These data suggest that the patient sample follows the profile one would expect in CFS, that is the group consisted predominantly of middle-aged, married females. When considering the current state of health variable, the majority of patients fell into the ‘bad with some recovery’ category (43%). These data were accompanied by a mean total symptom score (calculated from the 28-item check list) of 15.84 (s.e.m=0.36). The mean illness length for the patient group was approximately 5 years.

Insert Table 1 about here
The majority of patients (84%) believed that a specific event had proceeded and, therefore, may have caused the onset of the illness. Influenza was named as the main causal agent (42%). In addition, 68% of the group had their condition diagnosed by their GP and only 34% of the sample was in employment at the time of initial assessment. Of the remainder, 49% were unemployed, 16% were on sick leave and 24% were either retired or homemakers. Of the patients who were employed, 21% believed that their job security was threatened by the illness.

The participants were also asked if they had tried any alternative therapies to alleviate their symptoms. 94% reported that they had and had spent on average £235 doing so (range=0 to £4000). Less than half of these patients believed that they had received value for money by taking the alternative therapy route.

Next the sample were re-examined in terms of type of illness onset (acute or gradual onset). There was no evidence to suggest a difference between the groups in terms of the demographic nature of the illness, illness length or total symptom scores. In addition, we found no evidence to suggest that there might be a link between type of onset (acute or gradual) and the patient’s belief that a virus had caused the illness.

Individual Symptoms
Table 2 describes the 28-item symptom check-list for the patient group at baseline in further detail.

Insert Table 2 about here
These data indicate that muscle pain, lack of concentration and excessive fatigue were the highest rated symptoms in the patient group.

Validation of the Health Status Measure
Table 3 describes the relationship between the items of the current state of health (CSH) scale and other health-related measures known to be associated with CFS. As there were only two patients who fell into the ‘almost completely recovered’ item on the scale (item 5), we merged them with the ‘recovering with occasional relapses’ group. These data indicate a strong link between the items of the scale and the level of impairment present in CFS. Patients with a more positive and a less negative mood were significantly more likely to be in better health at baseline. There was also an association between lower levels of fatigue, somatic symptoms, physical symptoms and total symptoms and better health status at baseline. Furthermore, the impact of
psychosocial factors such as daily hassles and positive life events were evident in patients with poor health.

Insert Table 3 about here

To investigate these findings further, patients were split into two groups; those who were 'recovering' (items 4 and 5 on the current state of health scale) and those who were 'not recovering' (items 1, 2 and 3). Table 4 presents data describing the relationship between recovery and other health-related measures at baseline.

Insert Table 4 about here

These data provides clear-cut differences between the 'recovering' and 'not recovering' groups in terms of mood, psychopathology and symptoms at baseline. As these health-related measures are often associated with the severity of the illness the 'current state of health' variable also appears to accurately assess the true severity of the illness for each patient. In addition, psychosocial factors such as stress are thought to exacerbate the illness; patients with higher stress scores at baseline were significantly more likely to be in the 'not recovering' group.

**Longitudinal Patient Characteristics**

**Comparability of the Follow-up Sample**

To confirm that those patients who completed all aspects of the longitudinal study (n=130) were representative of the original cohort, we compared the baseline demographic scores for the two groups. Table 1 describes these data which suggest that there are no significant differences between the two groups in terms of gender, age, marital and educational status. In addition, there were no significant differences between the two samples in respect to length of illness, health status and total symptom scores at initial assessment (baseline).

**Recovery over time**

The item five of the current state of health variable provided data to suggest that very few patients will completely recover over time without treatment. Levels of spontaneous recovery were calculated at only 2% at six-month-follow-up and rose to 6% at 18 months later. This level of recovery remained unchanged at three-year follow-up.

When recovery was assessed in terms of 'recovery with occasional relapses' or to have 'almost completely recovered', 38% of patients were found to be in this category at six-month follow-up and this rose to 45% at three-year follow-up.

As the number of patients who had almost completely recovered at three years imposed statistical limitations for further analyses, recovery with occasional relapses was used in subsequent analyses.

**The Relationship between baseline Illness Characteristics and Recovery**

The next set of analyses examined whether baseline measures predicted subsequent recovery.

There was no association between age (using inter-quartile ranges) and subsequent recovery or illness onset type (acute or gradual) and recovery. Similarly, there was no indication from these data that physical or non-physical cause was associated with subsequent recovery. There was also no association between illness length at baseline and recovery at three-year follow-up. To investigate this further, illness length was further split into quartiles and cross-tabulated with the recovery variable. These data did indicate a trend for patients in the lowest quartile illness length group to have an increased likelihood of recovery at three year follow-up but this did not reach significance (p=0.056).
When comparisons were made between employment status and recovery, patients who were in employment at initial clinic visit (baseline) were significantly more likely to be in the recovered group at three-year follow-up (employed at baseline/recovered at three years=65.6%, employed at baseline/not recovered at three years=34.4%, $\chi^2 = 6.227$, df=1, p<0.011).

In addition, there was a significant association between health status at baseline and recovery at three-year follow-up ($\chi^2 = 23.554$, df=1, p<0.001). That is to say, those patients who reported better health status initially were more likely to recover.

The Relationship between Symptoms and Recovery

Again these data were split into quartiles and cross-tabulated with the recovery variable.

Patients with the highest fatigue and somatic symptoms scores were significantly less likely to recover at three-year follow-up (fatigue; $\chi^2 = 8.602$, df=3, p<0.035 and somatic symptoms; $\chi^2 = 9.359$, df=3, p<0.025). Similarly, patients recording the highest levels of physical symptoms at baseline were significantly less like to recover over three years ($\chi^2 = 11.408$, df=3, p<0.01). In addition, those who reported total symptom scores in the highest quartile range at baseline were significantly less likely to recover over time ($\chi^2 = 8.599$, d=3, p<0.035).

These results support the view that patients with milder illnesses are more likely to recover.

The Relationship between Mood, Psychopathology and Cognition at Baseline and Recovery

The relationship between mood and psychopathology at baseline and subsequent recovery was examined by splitting each measure into quartiles and conducting cross-tabulation analyses with the recovery variable.

Patients with the highest positive mood scores at baseline were significantly more likely to be in the recovering group at three-year follow-up ($\chi^2 = 8.896$, df=3, p<0.031). However, the same was not true for negative mood and recovery.

There was no association between psychopathology at baseline and recovery at three-year follow-up. In addition, there was no association between the levels of emotional distress and cognitive difficulties at baseline and subsequent recovery. Similarly, there was no association between baseline levels of perceived stress or impaired cognition and recovery.

DISCUSSION

The aims of the current study included the description of the demographic and illness characteristics of a large group of Chronic Fatigue Syndrome (CFS) patients at initial assessment (baseline) and the validation of a measure, developed by the research team in previous studies, to accurately evaluate health status at any given time point. The study also aimed to describe recovery in the untreated condition and to identify factors which influence and predict positive outcome.

The patients recruited onto the volunteer panel were consecutive GP referrals to a dedicated research clinic and were categorised by the Centre for Disease Control case definition for CFS [1]. The demographic data of the sample follows a similar profile to patients described by others, that is, the group comprised predominantly married, middle-aged women [21].

There has, in the past, been some debate as to whether an association between social classification and increased cases of Chronic Fatigue Syndrome exists [21, 22, 23]. Data from the current research indicates that the majority of the sufferers recruited to the study were grouped in the professional or semi-professional social categories.
confirming the association between the illness and a specific social grouping. This could, of course, reflect the method of recruiting the patients. The persistent and debilitating nature of the illness was demonstrated by a mean history length of five years and, on average, 16 individual symptoms present. One would expect total symptom scores of 3 from a group of healthy controls (submitted manuscript). The myriad symptoms associated with CFS are also indicated here; lack of concentration, muscle pain, excessive fatigue, physical weakness and legs feeling heavy were reported in over 80% of the cases. The length and severity of the illness is also reflected in the high numbers of patients who were either unemployed or on sick leave at initial assessment (baseline).

The health status of the patient group was assessed by the 5-item current state of health variable [11]. Applying this measure at baseline showed that the health status for the cohort was poor; the majority of the group (43%) rating their health as 'bad with some recovery'. Further analyses also suggested that the health status variable correlated with other illness-related measures at baseline such as total symptoms scores, mood, fatigue, psychopathology and stress. Considering that the patients described in the current study represented different stages of the illness in terms of severity and illness length, one might presuppose a link between the current state of health variable and the length of illness measure. That is to say, either patients with longer illness length could be categorised as having greater illness severity or conversely, after a certain length of time, the patient begins to recover. This, however, did not appear to be the case, with analyses showing that illness length (represented by quartile ranges) was equally spread over the 5-items of the health status measure.

When comparing items of the current state of health score and other health-related measures we were able to provide statistical evidence that the more severe items on the scale were associated with the more negative health measures. The health-related measures are not an indication of function or disability and, therefore, may not accurately reflect recovery. Although this is acknowledged as a limitation of the current study we did apply the same analyses to data collected as part of a treatment trial reported elsewhere [24, 25]. When assessing treatment efficacy we used the primary outcome measure adopted by Sharpe and his colleagues in their Cognitive Behaviour Therapy (CBT) trial [26]. By comparing the current state of health variable to this functional performance scale trial data we found a statistical significance between the two measures, that is, improved functioning was accompanied by better state of health scores ($\chi^2=18.937$, df=8, p<0.015). In the same treatment trial, 83.3% of the patients in the active arm of the study reported improvement in the state of health score ($\chi^2=9.78$, df = 4, p<0.044) post-therapy [24]. The validated current state of health measure was then used to assess recovery. Spontaneous recovery rates for the group were low at only 2% at six month follow-up. Furthermore, these rates did not improve a great deal eighteen months or three years later (6%). It is important to note at this point the relatively high drop-out rate over the follow-up period and acknowledge this a study limitation as those who did not respond to the three-year follow-up call may have recovered and felt no need to reply. This may have resulted in the recovery rates reported here being much lower than those seen in previous studies [6]. This said, our data are in-keeping with results from a recent review by Cairns & Hotopf [9] and a patient survey conducted by Thomas & Smith [27], which indicated that the occurrence of complete spontaneous recovery from CFS is, in fact, relatively rare.
When recovery was measured using a lax criterion, values increased allowing us to investigate possible predictors of recovery. Illness status at baseline significantly influenced recovery over time. Lower total symptom scores at baseline were associated with more favourable outcomes. There was also a trend, although not statistically significant, for shorter illness length to be linked with recovery. Overall, these data re-enforce the well held belief that diagnosing CFS effectively and setting coping and/or management strategies in place swiftly are vital to prevent the entrenchment of negative illness perceptions in patients and help facilitate positive outcome.

However, there was no evidence to suggest that physical cause attribution was associated with outcome or that type of onset (acute or gradual) affected prognosis. Furthermore, there was no evidence from these data to suggest that co-morbid anxiety or depression at baseline was associated with recovery in the longer term. Physical cause, illness onset type and co-existing psychopathology have been previously cited as possible factors affecting recovery in this patient group [8, 9]; data from the current study failed to provide evidence for such associations. The present study did show an association between employment status at baseline and subsequent recovery. Patients in employment at baseline were more likely to be in the recovered group at baseline, eighteen months and three years later. These data can be interpreted in two ways, (a) employment brings with it a sense of belonging and maintains levels of social support which prevents feelings of isolation which may in turn exacerbate the illness, or (b) patients in employment may be able to continue working because they have better health scores and these data may simply be reflecting illness severity.

CONCLUSIONS
The current longitudinal study has provided results indicating that prognosis for the untreated CFS patient is poor. Associations between the state of health measure and other physical and mental health variables have been verified using a large group of patients. The validation of a simple 5-item measure by other standardised measures leads us to believe that this score can be used to accurately rate patient illness severity. We have also shown that this measure can predict and assess recovery. Positive outcome measures were indicated in cases where illness length was short and when the number and severity of symptoms were low. We have confirmed the widely held belief among healthcare professionals that offering care to this patient group before the illness is allowed to become entrenched is of major importance if sustainable recovery is to be achieved.

COMPETING INTERESTS
The author(s) declare that they have no competing interest.

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REFERENCES
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Table 1: Baseline Demographic and Illness History data for the original cohort of CFS patients and the final cohort who completed the study.

<table>
<thead>
<tr>
<th>Baseline Measures</th>
<th>Original Cohort (n=226)</th>
<th>Final Cohort (n=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31%</td>
<td>34%</td>
</tr>
<tr>
<td>Female</td>
<td>69%</td>
<td>66%</td>
</tr>
<tr>
<td><strong>Mean Age:</strong></td>
<td>41.7 (0.80)</td>
<td>45.05 (1.15)</td>
</tr>
<tr>
<td><strong>Marital Status:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>21%</td>
<td>10%</td>
</tr>
<tr>
<td>Married</td>
<td>65%</td>
<td>75%</td>
</tr>
<tr>
<td>Divorced/ Separated</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>Widowed</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Educational Status:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Formal schooling</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Primary Education only</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Secondary Education</td>
<td>29%</td>
<td>30%</td>
</tr>
<tr>
<td>O Levels</td>
<td>33%</td>
<td>31%</td>
</tr>
<tr>
<td>A Levels</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>At least 1yr at University</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>BSc or BA</td>
<td>16%</td>
<td>17%</td>
</tr>
<tr>
<td>MSc or MA</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>PhD, MD, etc</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Illness Duration (months):</strong></td>
<td>62.13 (3.84)</td>
<td>65.49 (5.83)</td>
</tr>
<tr>
<td><strong>Current State of Health:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worse than at any stage</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Bad</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Health:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bad with some recovery</td>
<td>43%</td>
<td>43%</td>
</tr>
<tr>
<td>Recovering with relapses</td>
<td>38%</td>
<td>36%</td>
</tr>
<tr>
<td>Almost completely recovered</td>
<td>0.9%</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total Symptom Score (maximum = 28):</strong></td>
<td>15.84 (0.36)</td>
<td>16.32 (0.59)</td>
</tr>
</tbody>
</table>
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**Table 2:** The Symptom Checklist Scores for the patient group at baseline.
Scores are ranked most to least prevalent.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>%</th>
<th>Symptom</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of concentration</td>
<td>91</td>
<td>Sore throat</td>
<td>52</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>89</td>
<td>Wind</td>
<td>49</td>
</tr>
<tr>
<td>Excessive fatigue</td>
<td>87</td>
<td>Insomnia</td>
<td>47</td>
</tr>
<tr>
<td>Physical weakness</td>
<td>81</td>
<td>Nausea</td>
<td>46</td>
</tr>
<tr>
<td>Legs feeling heavy</td>
<td>80</td>
<td>Shivering</td>
<td>45</td>
</tr>
<tr>
<td>Fever</td>
<td>77</td>
<td>Glands swollen</td>
<td>45</td>
</tr>
<tr>
<td>Loss of memory</td>
<td>76</td>
<td>Racing heart</td>
<td>44</td>
</tr>
<tr>
<td>Headache</td>
<td>70</td>
<td>Chest pain</td>
<td>44</td>
</tr>
<tr>
<td>Aching joints</td>
<td>69</td>
<td>Indigestion</td>
<td>41</td>
</tr>
<tr>
<td>Sensitivity to noise</td>
<td>59</td>
<td>Panic attacks</td>
<td>40</td>
</tr>
<tr>
<td>Bloated stomach</td>
<td>55</td>
<td>Depression</td>
<td>37</td>
</tr>
<tr>
<td>Sweating</td>
<td>54</td>
<td>Allergies</td>
<td>35</td>
</tr>
<tr>
<td>Sore eyes</td>
<td>53</td>
<td>Earache</td>
<td>33</td>
</tr>
<tr>
<td>Sensitivity to light</td>
<td>53</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3: The relationship between the items of the Current State of Health measure and ratings of mood, fatigue, somatic symptoms, physical symptoms, total symptom, positive life events and daily hassles (quartiles) at baseline. Values are the percentage of patients within each item of the current state of health measure for each quartile range.

<table>
<thead>
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<th>Item 3</th>
<th>Item 4 &amp; 5</th>
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<td>38.6</td>
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<td>33.3</td>
<td>24.0</td>
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<td>40.0</td>
<td>24.0</td>
<td>10.9</td>
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<tr>
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<td>Total Symptoms</td>
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<tr>
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<td>11.1</td>
<td>55.3</td>
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<td>Daily Hassles:</td>
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<td>22.2</td>
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<td>Intensity</td>
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<td>33.3</td>
<td>28.9</td>
<td>21.6</td>
<td>17.7</td>
<td></td>
</tr>
</tbody>
</table>

Item 1=worse than at any stage; item 2=bad; item 3=bad with some recovery; item 4=recovering with occasional relapses; item 5=almost completely recovered.
3.5 Paper 5

Table 4: The relationship between Current State of Health and mood, psychopathology, symptoms and stress at baseline. ‘Recovering with occasional relapses’ and ‘Almost completely recovered’ represent the ‘Recovering’ group, the remaining values represent the ‘not recovering’ group. Values are the group means with s.e.m in parenthesis.

<table>
<thead>
<tr>
<th>Baseline Measures</th>
<th>Baseline Current State of Health</th>
<th></th>
<th></th>
<th>t, df, p</th>
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<td>Not Recovering</td>
<td>Recovering</td>
<td></td>
<td>t, df, p</td>
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<td>Positive Mood</td>
<td>24.75 (0.66)</td>
<td>28.16 (1.05)</td>
<td>-2.808, 296,</td>
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</tr>
<tr>
<td>Negative Mood</td>
<td>25.28 (0.83)</td>
<td>20.87 (1.02)</td>
<td>&lt;0.005</td>
<td>3.103, 297, &lt;0.002</td>
</tr>
<tr>
<td>Depression</td>
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<td>38.21 (1.02)</td>
<td>3.102, 295, &lt;0.002</td>
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<tr>
<td>State Anxiety</td>
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<td>38.21 (0.98)</td>
<td>2.497, 297, &lt;0.013</td>
<td></td>
</tr>
<tr>
<td>Emotional Distress</td>
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<td>42.96 (2.02)</td>
<td>2.630, 297, &lt;0.009</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>67.09 (0.91)</td>
<td>53.83 (1.73)</td>
<td>7.432, 295, &lt;0.001</td>
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<tr>
<td>Cognitive Difficulties</td>
<td>49.26 (1.06)</td>
<td>41.80 (1.73)</td>
<td>3.796, 297, &lt;0.001</td>
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<tr>
<td>Somatic Symptoms</td>
<td>56.89 (1.38)</td>
<td>45.05 (1.73)</td>
<td>5.004, 295, &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Physical Symptoms</td>
<td>27.072 (0.54)</td>
<td>19.99 (0.80)</td>
<td>7.236, 296, &lt;0.001</td>
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<tr>
<td>Total Symptoms</td>
<td>16.73 (0.37)</td>
<td>13.62 (0.55)</td>
<td>4.674, 300, &lt;0.001</td>
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<tr>
<td>Perceived Stress</td>
<td>27.45 (0.61)</td>
<td>25.22 (0.75)</td>
<td>2.132, 296, &lt;0.034</td>
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</tbody>
</table>
An investigation of the long-term benefits of antidepressant medication in the recovery of patients with chronic fatigue syndrome

Marie A. Thomas* and Andrew P. Smith

Centre for Occupational and Health Psychology, School of Psychology, Cardiff University, UK

Two hundred and seventy-five patients fulfilling the Centre for Disease Control (CDC) criteria for Chronic Fatigue Syndrome (CFS) completed measures assessing illness history, global ratings of well being, sleep, activity and psychopathology at baseline, 6 months, 18 months and 3 year follow-up. Forty-nine of these patients had been prescribed antidepressant medication, namely Tricyclic or Selective Serotonin Re-uptake Inhibitors (SSRI). Data from the current study suggests that patients in the antidepressant medication group recover at a faster rate over time when compared to the untreated patient sample. In addition, the positive effects of antidepressant therapy are maintained at the 3-year follow-up point. It appears from these data that the SSRI in particular are responsible for improvements in the condition. Most importantly, these improvements include a reduction in the levels of fatigue recorded by patients. These findings have not been demonstrated in previous studies of the effect of antidepressant therapy for patients with this illness and this may reflect the short time periods studied in the earlier research. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS — Chronic Fatigue Syndrome; antidepressant medication; recovery

INTRODUCTION

Fatiguing illnesses, in particular Chronic Fatigue Syndrome (CFS), are difficult conditions to accurately determine and quantify. Holmes et al. (1988) developed a working case definition for CFS, which provided a structured method for categorising the illness. Modified definitions such as the Oxford criteria, as described by Sharpe and colleagues (1991), and the Centre for Disease Control (CDC) criteria (Fukuda et al., 1994) have added coherence and further guidelines for clinicians and researchers in the field. These criteria define a person suffering from CFS as one who has experienced persistent, debilitating fatigue for 6 months or more. Rest, in these patients, is not restorative and the fatigue state is not due to ongoing exertion. Onset is described here as 'definite' or 'new' and there may be several co-existing symptoms present. The physical fatigue experienced in CFS produces a marked reduction in activity, and together with other ancillary symptoms such as pain and sleep disturbance, make the illness debilitating and persistent (Andersen et al., 2004). The resulting illness leads to a substantial decrease in personal, social and occupational activities, severely affecting the patient’s quality of life.

Both the cause of CFS and the mechanisms that maintain it remain largely unknown. Surawy et al. (1995) produced data suggesting that once the illness had established itself, cognitive, behavioural, emotional, physiological and social factors might work together to perpetuate it. Due to the complexity of the illness possible treatments have, therefore, been investigated on a pragmatic basis. Several centres have reported results from pharmacological based treatment studies which focused on agents that alleviate some of the symptoms associated with CFS (Goodnick et al., 1992; Vercoulen et al., 1996; Hickie et al., 1999 for example). These include symptoms such as co-morbid anxiety and depression and problems of

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sleep disturbance which are often associated with CFS and other medically unexplained syndromes (O’Malley et al., 1999). However, results from previous studies have been mixed, and although antidepressant therapy has been shown successful in terms of alleviating certain symptoms associated with the syndrome, there is no firm evidence to suggest that they facilitate recovery in CFS. In an in-depth review of treatments for CFS by Rimes and Chalder (2005), three randomised controlled trials (RCT) of two antidepressants; the Selective Serotonin Re-uptake Inhibitor (SSRI) fluoxetine (Vercoulen et al., 1996) and the Monoamine-oxidase Inhibitor (MAOI) phenelzine (Natelson et al., 1996), were discussed. Two of the RCTs reviewed, did not provide significant results for any of the outcome measures used in the trial; the third, again using fluoxetine (Wearden et al., 1998) showed modest improvements in the level of depression expressed by patients in the antidepressant group but no positive effect on fatigue. There was no evidence to suggest that these agents provided any useful purpose in the treatment of CFS.

However, both therapy length and follow-up assessment point for the treatment trials described above were relatively short. For example, in the study conducted by Hickie (1999), nefazodone was administered to patients for a 6-week period followed immediately by the collection of the final assessment measures. Similarly, in the RCT described by Vercoulen et al. (1996), fluoxetine was administered to CFS sufferers for 8 weeks with a final data collection point 2 months post-therapy. It may be the case that both pharmacological intervention and final outcome data should be conducted over a longer time frame for any measurable improvement to become apparent. To illustrate this, studies conducted by Antelman and his colleagues (Antelman and Gershon, 1998 for example) suggested that the positive effects of antidepressant medication for major depressive illnesses continue and improve long after the cessation of treatment. In addition, this phenomenon, termed time-dependent sensitisation to antidepressant therapy, was indicated following even single treatments. It would, therefore, be of interest to follow CFS patients prescribed antidepressant medication over a longer time period.

Data collection for the current study formed part of an ongoing research programme investigating the characteristics and natural progression of CFS. Initial findings had already highlighted impairments associated with the illness such as mood and other psychopathological disturbance (Smith et al., 1996). These problems became evident when comparing the patient group with an age, gender and educationally matched healthy control group using a wide-ranging battery of questionnaires. Furthermore, these data were also collected at specific follow-up points in order to chart the typical illness history of these patients. Improvements in health-related measures taken at baseline could, therefore, be used to estimate recovery rates in the untreated patient over time. Once validated, these data provided a measure which could accurately evaluate patients’ health status. In addition, the same measure was used to assess recovery from the condition and evidence from these studies suggested that spontaneous recovery from CFS is relatively rare at only 6% at 3-year follow-up.

When describing these data it was discovered that a small proportion of the patient sample recruited for the study had been prescribed antidepressant medication, either Tricyclic or SSRI antidepressants, at the time of referral. It was considered, therefore, that it would be of interest to investigate retrospectively the role antidepressant therapy plays in the recovery in the otherwise untreated patient. To achieve this, data from this sub-group of patients were compared to those patients not prescribed antidepressant medication in an attempt to provide evidence of the possible efficacy of these agents in recovery.

METHODS AND MATERIALS

Ethical approval was granted by the appropriate local Health Authority. All participants gave informed consent and data was coded to protect the anonymity of the patients.

Design

Data were collected longitudinally over a period of 3 years. The design was mixed, with the between-subject factor being antidepressant status and the within-subjects factor the various time points at which testing took place, that is, baseline, 6 months, 18 months and 3 years. Two sets of analyses were performed, one comparing health status (recovering or not recovering) in patients taking antidepressant medication with those taking no antidepressants, the other analysis compared, again, health status, but this time looking at differences between patients taking Tricyclic antidepressants, patients taking SSRI antidepressants and those taking no antidepressants.
Participants
Patients attending a dedicated outpatient clinic fitting the CDC criteria for CFS (Fukuda et al., 1994) were invited to join a research panel. Each patient completed a comprehensive range of questionnaires charting illness history and psychopathology. At the clinic, research registrars conducted a detailed examination of each patient’s medical history, including previous and current antidepressant medication history.

Questionnaires
A comprehensive range of measures was administered, including standardised demographic measures, a brief illness history questionnaire and a 28-item symptom check list (Smith et al., 1996). The Beck Depression Inventory (Beck et al., 1961) and the Spielberger Trait Anxiety Inventory (Spielberger et al., 1971) were used to measure co-morbid depression and anxiety in this study and fatigue was also measured using the fatigue sub-scale of the Profile of Fatigue Related Symptoms (PFRS) questionnaire (Ray et al., 1993). Recovery was calculated using the current state of health variable (Smith et al., 1996). This self-rated five-item scale describes the current illness as: (a) worse than at any stage, (b) bad, (c) bad with some recovery, (d) recovering with occasional relapses and (e) almost completely recovered. Recovery was assessed by calculating changes in this measure over time. Sleep quality and activity levels were measured using individual five-item scales with responses ranging from 'much worse' to 'much better' (Smith et al., 1996).

The questionnaires were completed at baseline, and then repeated again at 6 months and 3 years later. In addition, a shortened questionnaire, comprising the symptom check list and current state of health scale, was completed 18 months after the baseline measures.

Data analysis
A series of Chi-squared analyses were conducted on catoric demographic variables and one-way analysis of variance (ANOVA) tests were conducted on continuous data at baseline. Analysis of variance and independent sample t-tests were conducted to highlight any differences between the groups over time.

RESULTS
Data revealed that 17% of the cohort had been prescribed antidepressants at baseline. Approximately half of those taking antidepressants had been prescribed Tricyclics (53%) and the rest SSRI (47%). 61% of these individuals indicated that antidepressant therapy had been helpful in alleviating their symptoms. When considering illness onset type (gradual or acute), the acute onset sub-group was marginally less likely to be taking antidepressant medication than the gradual onset group (p = 0.07). There were no associations between illness length and likelihood of taking antidepressant medication.

Firstly we considered antidepressant group as a whole. Table 1 describes the baseline demographic and illness history data for the antidepressant and no-antidepressant groups. These data reveal that there are no significant differences between the two groups at baseline.

Furthermore, data from the 28-item symptom check list provided little evidence of significant differences between the two groups at baseline (see Table 2). The one exception being that the antidepressant group were significantly more likely to rate depression as a symptom (p < 0.01).

Independent sample t-test analyses provided no evidence to suggest that there were any differences between the two groups for any of the other measures recorded at baseline, including questionnaire measures of anxiety and depression.

At follow-up, however, several differences emerged. When recovery was considered (using the current state of health measure) the antidepressant group record greater recovery rates over time than the no-antidepressant group and these data reach significance at 3 years (p < 0.03; see Table 3).

This profile of recovery is also indicated in terms of total symptom scores. In other words, there was a significant lowering of total symptom scores in the antidepressant group compared to the no-antidepressant group (see Table 4).

If we look at individual symptoms, significant differences were reported between the two groups at 18 month and 3 year follow-up as shown in Table 5.

These data suggests that patients taking antidepressant medication at baseline were significantly less likely to report symptoms, such as physical weakness, physical fatigue, aching joints and allergies at follow-up than the no-antidepressant group. There was also a marginal difference in the reporting of lack of concentration as a symptom in these patients at 3-year follow-up (p = 0.06). The fatigue sub-scale of
the PFRS also indicates a significant difference in the level of fatigue experienced by the antidepressant group at 6 months (antidepressants = 53.97; no- antidepressants = 60.00; t = 1.97, df = 184, p < 0.05) and 3 years (antidepressants = 49.71; no- antidepressants = 58.17; t = 2.03, df = 118, p = 0.04), indicating that the antidepressant group were reporting lower levels of fatigue than the no-antidepressant group.

In addition, patients in the antidepressant group were significantly more likely to report improvements in quality of sleep over the 6-month follow-up period (antidepressants = 24%; no-antidepressants = 5%; $\chi^2 = 9.89$, df = 2, $p < 0.001$) and at 3-year follow-up.

### Table 1. Demographic data for the antidepressant/no-antidepressant patient groups at baseline

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<th>Baseline measure</th>
<th>No-antidepressant (n = 226)</th>
<th>Antidepressant (n = 49)</th>
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<td>Gender:</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>31%</td>
<td>20%</td>
</tr>
<tr>
<td>Female</td>
<td>69%</td>
<td>80%</td>
</tr>
<tr>
<td>Age</td>
<td>42 (0.80)</td>
<td>44 (1.37)</td>
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<td>Marital status:</td>
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<tr>
<td>Single</td>
<td>21%</td>
<td>19%</td>
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<tr>
<td>Married</td>
<td>66%</td>
<td>67%</td>
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<tr>
<td>Divorced/separated</td>
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<td>8%</td>
</tr>
<tr>
<td>Widowed</td>
<td>3%</td>
<td>6%</td>
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<tr>
<td>Employment status:</td>
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<tr>
<td>Employed</td>
<td>28%</td>
<td>26%</td>
</tr>
<tr>
<td>Unemployed</td>
<td>40%</td>
<td>33%</td>
</tr>
<tr>
<td>On sick leave</td>
<td>13%</td>
<td>25%</td>
</tr>
<tr>
<td>Other (homemaker/retired)</td>
<td>19%</td>
<td>16%</td>
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<tr>
<td>Illness history and beliefs:</td>
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<td></td>
</tr>
<tr>
<td>Acute</td>
<td>63%</td>
<td>50%</td>
</tr>
<tr>
<td>Gradual</td>
<td>37%</td>
<td>50%</td>
</tr>
<tr>
<td>Illness duration (months)</td>
<td>62.1 (3.84)</td>
<td>65.9 (7.41)</td>
</tr>
<tr>
<td>Total symptom scores (maximum = 28)</td>
<td>15.8 (0.36)</td>
<td>15.5 (0.84)</td>
</tr>
<tr>
<td>Viral cause (suggested by patient)</td>
<td>65%</td>
<td>58%</td>
</tr>
<tr>
<td>Specific event</td>
<td>84%</td>
<td>90%</td>
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</table>

### Table 2. Individual Symptoms for the antidepressant/no-antidepressant groups at baseline expressed as the percentage reporting the symptom

<table>
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<tr>
<th>Symptom</th>
<th>No antidepressant</th>
<th>Antidepressant</th>
<th>Symptom</th>
<th>No antidepressant</th>
<th>Antidepressant</th>
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<tr>
<td>Physical weakness</td>
<td>81.4</td>
<td>81.6</td>
<td>Sensitivity to noise</td>
<td>58.8</td>
<td>61.2</td>
</tr>
<tr>
<td>Physical fatigue</td>
<td>86.7</td>
<td>81.6</td>
<td>Sensitivity to light</td>
<td>52.7</td>
<td>44.9</td>
</tr>
<tr>
<td>Legs feeling heavy</td>
<td>80.1</td>
<td>75.5</td>
<td>Fever</td>
<td>77.4</td>
<td>79.6</td>
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<tr>
<td>Muscle pain</td>
<td>89.4</td>
<td>89.8</td>
<td>Sweating</td>
<td>54.4</td>
<td>61.2</td>
</tr>
<tr>
<td>Chest pain</td>
<td>43.8</td>
<td>34.7</td>
<td>Shivering</td>
<td>43.8</td>
<td>40.8</td>
</tr>
<tr>
<td>Aching joints</td>
<td>69.0</td>
<td>65.3</td>
<td>Swollen glands</td>
<td>45.1</td>
<td>38.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>46.0</td>
<td>36.7</td>
<td>Racing heart</td>
<td>45.1</td>
<td>46.9</td>
</tr>
<tr>
<td>Indigestion</td>
<td>39.8</td>
<td>34.7</td>
<td>Insomnia</td>
<td>47.3</td>
<td>53.1</td>
</tr>
<tr>
<td>Stomach feeling bloated</td>
<td>53.1</td>
<td>53.1</td>
<td>Depression</td>
<td>36.7</td>
<td>55.1*</td>
</tr>
<tr>
<td>Wind</td>
<td>49.1</td>
<td>44.9</td>
<td>Feelings of panic</td>
<td>41.2</td>
<td>42.9</td>
</tr>
<tr>
<td>Sore throat</td>
<td>52.2</td>
<td>51.0</td>
<td>Loss of concentration</td>
<td>90.7</td>
<td>83.7</td>
</tr>
<tr>
<td>Headache</td>
<td>69.9</td>
<td>73.5</td>
<td>Loss of memory</td>
<td>75.7</td>
<td>75.5</td>
</tr>
<tr>
<td>Earache</td>
<td>32.7</td>
<td>20.4</td>
<td>Allergies</td>
<td>35.4</td>
<td>28.6</td>
</tr>
<tr>
<td>Sore eyes</td>
<td>54.9</td>
<td>61.2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* $\chi^2 = 5.67$, df = 1, $p < 0.014$.  

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Table 4. Total Symptom scores for the antidepressant/no-antidepressant groups at baseline, 6 month and 3 year follow-up. Scores are the group means with s.e.m in parenthesis (maximum score = 28).

<table>
<thead>
<tr>
<th>Total Symptoms</th>
<th>No Antidepressant</th>
<th>Antidepressant</th>
<th>F, df, p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>15.84 (0.36)</td>
<td>15.47 (0.84)</td>
<td>n/h</td>
</tr>
<tr>
<td>6 months</td>
<td>14.90 (0.49)</td>
<td>13.60 (1.07)</td>
<td>n/h</td>
</tr>
<tr>
<td>18 months</td>
<td>14.67 (0.46)</td>
<td>12.24 (1.13)</td>
<td>4.671, 1,213, p &lt; 0.032</td>
</tr>
<tr>
<td>3 years</td>
<td>15.12 (0.59)</td>
<td>11.75 (1.29)</td>
<td>6.281, 1,119, p &lt; 0.014</td>
</tr>
</tbody>
</table>

up (antidepressants = 29%; no-antidepressants = 7%; \( \chi^2 = 9.89, df = 2, p < 0.007 \)). Furthermore, patients in the antidepressant group reported higher activity levels than the no-antidepressant group (antidepressants = 21%; no-antidepressants = 4%; \( \chi^2 = 9.89, df = 2, p < 0.02 \)).

To investigate these findings further, the group of patients taking antidepressant medication were split into those taking the Tricyclic and related group of antidepressants and those taking SSRI and again compared to the no-antidepressant group.

Again there were no significant differences between the demographic nature of three groups at baseline or in the type of illness onset (acute or gradual) and duration. Patients in the SSRI group were significantly more likely to be in employment at baseline than the Tricyclic or no-antidepressant groups (SSRI = 49%, Tricyclic = 15%, no-antidepressant = 28%; \( \chi^2 = 6.34, df = 2, p < 0.04 \)). However, data from the current state of health measure indicated no difference in illness severity between the three groups at baseline.

In terms of recovery, patients in the SSRI group were marginally more likely to be in the 'almost completely recovered' section of the health status

Table 5. Individual Symptom Scores for the antidepressant/no-antidepressant groups at 18 months and 3 year follow-up. Scores are expressed as the percentage of patients reporting the symptom

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No antidepressant</th>
<th>Antidepressant</th>
<th>( \chi^2, p ) (df = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 months:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical fatigue</td>
<td>77</td>
<td>55</td>
<td>7.272, &lt;0.008</td>
</tr>
<tr>
<td>Chest pain</td>
<td>36</td>
<td>21</td>
<td>3.282, &lt;0.049</td>
</tr>
<tr>
<td>Aching joints</td>
<td>73</td>
<td>55</td>
<td>4.507, &lt;0.029</td>
</tr>
<tr>
<td>Noise</td>
<td>63</td>
<td>45</td>
<td>4.369, &lt;0.029</td>
</tr>
<tr>
<td>Light</td>
<td>56</td>
<td>32</td>
<td>7.268, &lt;0.006</td>
</tr>
<tr>
<td>Swelling</td>
<td>36</td>
<td>18</td>
<td>4.286, &lt;0.027</td>
</tr>
<tr>
<td>Allergies</td>
<td>32</td>
<td>8</td>
<td>9.291, &lt;0.001</td>
</tr>
<tr>
<td>3 years:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical weakness</td>
<td>79</td>
<td>50</td>
<td>8.538, &lt;0.005</td>
</tr>
<tr>
<td>Physical fatigue</td>
<td>75</td>
<td>50</td>
<td>5.873, &lt;0.017</td>
</tr>
<tr>
<td>Aching joints</td>
<td>76</td>
<td>54</td>
<td>4.660, &lt;0.031</td>
</tr>
<tr>
<td>Fever</td>
<td>73</td>
<td>50</td>
<td>4.805, &lt;0.028</td>
</tr>
<tr>
<td>Allergies</td>
<td>32</td>
<td>8</td>
<td>3.414, &lt;0.014</td>
</tr>
</tbody>
</table>

scale than the Tricyclic or no-antidepressant group at 6 months (\( p = 0.06 \)) and 18 months (\( p = 0.06 \)). These data did, however, reached significance at 3-year follow-up (SSRI = 43%, Tricyclic = 10%, no-antidepressant = 6%; \( \chi^2 = 22.07, df = 8, p < 0.005 \)). As reported in previous studies, there is an association between the current state of health variable with total symptom scores. Table 6 describes the mean total symptom scores at baseline, 6 and 18 months and 3 year follow-up points.

At baseline, patients in the Tricyclic antidepressant group reported significantly higher total symptom scores than the SSRI group. The total symptoms scores for both antidepressant groups were lowered at 18 months and 3-year follow-up compared to the no-antidepressant group but only the SSRI group reaches significance.

Again, there were differences in individual symptom reporting at 18 months and 3 years (Table 7).

It is clear from these data that it is specifically the SSRI group of patients who were responsible for the decreased reporting of symptoms such as physical weakness and fatigue and aching joints. The fatigue sub-scale of the PFRS questionnaire also confirms this by providing data to suggest that there is an improvement in fatigue scores in the SSRI group over time.

The quality of sleep measure indicated that there was a significant improvement at 3-year follow-up in the SSRI group (SSRI = 43%, Tricyclic = 10%, no-antidepressant = 7%; \( \chi^2 = 20.62, df = 4, p < 0.001 \)). Interestingly, this group also reported significantly increased activity levels at 3-year follow-up (SSRI = 29%, Tricyclic = 10%, no-antidepressant = 4%; \( \chi^2 = 11.50, df = 4, p < 0.02 \)).

There were no differences between any of the groups in terms of co-morbid anxiety and depression at baseline (Spielberger et al., 1971; Beck et al., 1961). In addition, there were no significant improvements in the psychopathology of these groups over the follow-up period. However, the significant difference between the groups when reporting depression as a major symptom (on the 28-item checklist) at baseline is lost at subsequent follow-up points.
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Table 6. The total symptom scores for the SSRI, Tricyclic and no-antidepressant groups at baseline, 6 months, 18 months and 3 year follow-up. Scores are the group means with s.e.m in parenthesis (maximum score = 28)

<table>
<thead>
<tr>
<th>Total symptoms</th>
<th>No antidepressant</th>
<th>SSRI (n = 23)</th>
<th>Tricyclic (n = 26)</th>
<th>P, df, p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>15.84 (0.36)</td>
<td>13.43 (0.89)</td>
<td>17.27 (1.28)</td>
<td>3.063, 2.272, p &lt; 0.048</td>
</tr>
<tr>
<td>6 months</td>
<td>14.90 (0.49)</td>
<td>13.09 (1.42)</td>
<td>14.23 (1.64)</td>
<td>n.s.</td>
</tr>
<tr>
<td>18 months</td>
<td>14.67 (0.46)</td>
<td>10.32 (1.38)</td>
<td>14.16 (1.72)</td>
<td>4.155, 2, 211, p &lt; 0.017</td>
</tr>
<tr>
<td>3 years</td>
<td>15.12 (0.59)</td>
<td>10.93 (1.70)</td>
<td>12.90 (2.03)</td>
<td>3.455, 2, 118, p &lt; 0.035</td>
</tr>
</tbody>
</table>

DISCUSSION

Data collection for the current study was conducted as part of a larger project aimed at charting the natural progression of CFS over time in a cohort of untreated patients. On referral to a specialised out-patient clinic, each patient completed a lengthy medical examination with medical staff who also recorded a detailed account of each patient’s illness history. When data collection was completed, descriptive analyses revealed that a small sub-group of patients (n = 49) had been prescribed antidepressant medication at the time of referral. The antidepressant therapy sub-group was comprised of patients who had been prescribed one of two antidepressant groups, namely the Tricyclic or SSRI antidepressants. An important feature of this study was to investigate the effect these agents had on CFS and whether antidepressant therapy does indeed assist recovery. To achieve this, data from the antidepressant medication sub-group were compared to that of the CFS sample as a whole (n = 226).

The baseline data indicated that there were no significant differences in the demographic nature of those patients taking antidepressant medication and those who were not. This was also true for the number of symptoms reported and health status of the two groups at baseline. This means that any differences seen at subsequent follow-up points can not be attributed to confounding variables such as age and gender differences or illness severity.

Data collected at follow-up suggests recovery rates of 10.5% in the antidepressant group at 6 months compared to only 2% in the non-antidepressant group. Furthermore, this recovery rate continued to improve over time reaching 29.2% by the 3-year follow-up point (compared to only 6% in the non-antidepressant group).

Previous studies had indicated that changes in the current state of health measure (used to assess recovery) were linked to changes in other health-related measures. For example, improvements in the health status measure were accompanied by a lowering in the total number of symptoms recorded. Data from the current study confirmed this association; the antidepressant group also reported fewer symptoms than the non-antidepressant group at follow-up. When considering the symptom checklist in terms of individual scores, the antidepressant group reported lower levels of physical weakness and fatigue and fewer cases of achings joints. Furthermore, a decrease in reporting depression as a major symptom was also observed in the antidepressant group over time. In addition this group also reported improvements in activity levels and quality of sleep over the follow-up period. Previous studies had indicated that psychomotor, memory and attention deficits reported in CFS

Table 7. Individual Symptom Scores for the SSRI, Tricyclic and no-antidepressant groups at 18 months and 3 year follow-up. Scores are expressed as the percentage of patients reporting the symptom

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No antidepressant</th>
<th>SSRI</th>
<th>Tricyclic</th>
<th>( \chi^2, p \ (df = 1) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 months:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical weakness</td>
<td>77</td>
<td>42</td>
<td>89</td>
<td>13.652, p &lt; 0.001</td>
</tr>
<tr>
<td>Physical fatigue</td>
<td>77</td>
<td>37</td>
<td>74</td>
<td>13.799, p &lt; 0.001</td>
</tr>
<tr>
<td>Aching joints</td>
<td>73</td>
<td>42</td>
<td>68</td>
<td>7.618, p &lt; 0.022</td>
</tr>
<tr>
<td>Light</td>
<td>56</td>
<td>21</td>
<td>42</td>
<td>8.954, p &lt; 0.011</td>
</tr>
<tr>
<td>Allergies</td>
<td>32</td>
<td>5</td>
<td>10</td>
<td>9.422, p &lt; 0.009</td>
</tr>
<tr>
<td>3 years:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical weakness</td>
<td>79</td>
<td>29</td>
<td>80</td>
<td>16.470, p &lt; 0.001</td>
</tr>
<tr>
<td>Physical fatigue</td>
<td>75</td>
<td>36</td>
<td>70</td>
<td>9.154, p &lt; 0.010</td>
</tr>
<tr>
<td>Aching joints</td>
<td>76</td>
<td>43</td>
<td>70</td>
<td>6.788, p &lt; 0.034</td>
</tr>
</tbody>
</table>

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appeared to reflect those seen in sleep disorders and physical de-conditioning (Smith et al., 1996). It could be that by addressing sleep quality, antidepressant therapy is facilitating recovery in this patient group.

The antidepressant group was further sub-divided into those taking Tricyclic antidepressants or SSRIs and compared again to the no-antidepressant group. Again, there were no differences between the three groups in terms of demographics or illness severity at baseline. Comparisons provided some interesting data; in particular, those results indicating improvements over time. These seem more favourable when focussing on the SSRRI antidepressant group. Forty-three per cent of this group reported their state of health as 'almost completely recovered' at the 3-year follow-up point. This was a considerable improvement when compared to the un-treated sample recovery rate of 6%. In addition, the SSRRI group recorded significant improvements in total symptom scores over time. Most importantly, these improvements were seen in symptoms such as physical weakness and fatigue which are two of the most common symptoms reported by sufferers in previous studies. In addition, patients with CFS typically report problems with sleep quality and maintaining levels of physical activity; the SSRRI antidepressant data indicated improvement in both areas.

One important drawback to the current study is its retrospective nature, we do not, therefore, possess information relating to the length of intervention, the dosage of medication or the specific drugs used. Similarly, we are unable to address the extent to which patients in the antidepressant group were a self-selecting subgroup of CFS. Anecdotal evidence suggests that patients with this illness are reluctant to take antidepressant medication and many report 'sensitivity' to them. However, even when one takes these factors into consideration, there was evidence to suggest that antidepressant medication, particularly the SSRIs, do, in fact, facilitate recovery in CFS. Furthermore, these improvements included a measurable reduction in level of fatigue suffered by patients, an outcome which has not been demonstrated previously.

Although the long-term practical benefits of antidepressant medication for patients with CFS are indicated by these findings further research into these positive effects is required. Two studies are indicated: (a) a comparison of patients prescribed long-term medication with those taking antidepressants for only short periods and (b) short-term antidepressant use followed by the long-term monitoring of their effects, which would replicate studies conducted by Antelman and Gershon (1998). In addition, patients would be randomly assigned antidepressant or placebo. In this way it may be possible to maximise the benefits of this type of medication for facilitating recovery in CFS using minimal intervention periods.

ACKNOWLEDGEMENTS

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REFERENCES


Primary healthcare provision and Chronic Fatigue Syndrome: a survey of patients' and General Practitioners' beliefs

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Abstract
Background: The current study was conducted as part of a research project into the evaluation and assessment of healthcare provision and education in Chronic Fatigue Syndrome (CFS). One aim of the study was the development of informative and educational literature for both General Practitioners (GP) and sufferers. Issues such as diagnosis, management and treatment of the syndrome should be included in information booklets written by healthcare professionals. It was important to begin the process by assessing the level of specialist knowledge that existed in typical GP surgeries. This data would then be compared to data from CFS patients.

Method: 197 survey booklets were sent to CFS sufferers from an existing research panel. The patients approached for the purpose of the study had been recruited onto the panel following diagnosis of their illness at a specialised CFS outpatient clinic in South Wales. A further 120 booklets were sent to GP surgeries in the Gwent Health Authority region in Wales.

Results: Results from the study indicate that the level of specialist knowledge of CFS in primary care remains low. Only half the GP respondents believed that the condition actually exists.

Conclusion: Steps are recommended to increase the knowledge base by compiling helpful and informative material for GPs and patient groups.

Background
A patient with Chronic Fatigue Syndrome (CFS) is described as one suffering unrelenting, debilitating fatigue (for a period of six months or more) which is unresolved by rest. This fatigue is not the result of normal physical activity and can cause both mental and physical impairment to the sufferer. Furthermore, the fatigue experienced is not as a result of an ongoing medical condition. Chronic Fatigue Syndrome remains a poorly understood condition and still poses problems in terms of causality, diagnosis and management for clinicians and researchers alike [1]. The myriad symptoms of the syndrome also present major diagnostic problems for primary healthcare providers. Unfortunately, lack of specialised knowledge (within the healthcare system) and scepticism on the part of some often leads to a breakdown in trust and confidence between patient and physician. This problem was highlighted in an investigation of perceptions in patients with CFS who had been referred to a specialised clinic [2]. 68 patients completed a survey assessing their satisfaction with the medical care offered at the clinic. Two-thirds of the sample expressed feeling dissatisfied with the quality of care received during their illness. Furthermore, these patients were more likely to describe delay, dispute or
confusion over diagnosis. Many of these same patients had received a psychiatric diagnosis for their symptoms which they rejected. In addition, this sub-group of patients perceived doctors as dismissive, sceptical or lacking in knowledge of CFS and felt that advice given was inadequate or conflicting. In contrast, satisfied patients believed doctors to be sympathetic and supportive of their condition. A major conclusion drawn from this study was the importance of understanding and effective communication between doctor and patient in dealing with CFS. Patients, it would seem, preferred GPs who, although admitting a lack of knowledge on the subject, offered empathy and support.

There are many avenues open to sources of information on CFS for doctors and patients alike. Unfortunately, too often they offer inaccurate and conflicting advice. In an age of increasing access to the internet, an Australian survey [3] reviewed 225 websites over a two week period. Widely differing views were found from websites offering information with regard to treatment for CFS. There was, however, general agreement that graded exercise and avoidance of prolonged rest were the most successful management strategies for sufferers. 64% of the sites offering advice had a named author. However, only a quarter to a third of the sites reviewed advised readers to clarify the information proffered with an appropriate health physician or avoided the inclusion of inaccurate statements. The report concluded that physicians should provide guidance for patients as to which internet sites to trust. It also recommended that GPs should be made fully aware of the nature of the information being accessed by patients. Misinformation leading to possible distress for the patient could then be avoided.

The strategies employed by physicians in Sweden, to categorise, diagnose and treat CFS and fibromyalgia (FM) patients was investigated by Åspring and Närvinen in 2003 [4]. During their study twenty-six physicians, all of whom had knowledge of working with CFS or FM, completed a semi-structured interview. Results from the study suggested that there was a discrepancy between the ideal role that the physician wished to fulfil and the reality of everyday work involving interaction with CFS patients. The physicians were concerned that their lack of specialist knowledge prevented them from providing proper healthcare support for their patients. This, the authors' concluded, led to the professional role being questioned by the patient. The point was also raised that some physicians were viewing CFS as a less serious illness than those conditions deemed to have 'disease status'. Further to this, scepticism was expressed on the part of the physicians as to the actual existence of CFS. Indeed, further studies have supported these findings [5]. It can be inferred from these studies, therefore, that there is continued diversity within the primary healthcare setting. Views ranging from questioning the existence of the syndrome to differing modes of diagnosis and management have been recently reported [5]. As an example of this, the Department of Public Health and Primary Care at the University of Hull conducted a national survey of General Practitioners (GP) and their beliefs regarding CFS [6]. Their research produced a comprehensive report on the current state of affairs within the United Kingdom. 300 questionnaires were sent out to GP surgeries in ten Regional Health Authorities in England, Scotland and Wales. Five of the Authorities surveyed had specialised centres for CFS, five did not. The five regions that did not have specialised centres for CFS were matched as closely as possible to those that did. One conclusion from the study indicated that although the GPs in the areas with specialised CFS clinics were more likely to belief that the condition existed, there was no difference in their 'propensity to diagnose' than those in areas without specialised services. This suggests that although GPs in the areas with specialised centres were aware of the clinics' existence, there was limited flow of specialist knowledge from the centres to primary care.

GPs' perceptions of patients with CFS have been studied in comparison with other syndromes. In 2004, Raine et al. [7] compared GP beliefs regarding patients with CFS to those with Irritable Bowel Syndrome (IBS). Their findings indicated that the attitudes of GPs to either CFS or IBS dictated subsequent management of the illness. The research concludes that these perceptions would ideally need to change to facilitate successful treatment implementation.

The aetiology, diagnosis, management and treatment for patients with CFS remain unclear and the need for further research into this condition is vital. This paper does in some cases set out to replicate the findings of other studies but was conducted as part of a wider research project investigating healthcare evaluation and patient education in CFS.

**Objectives of the present study**

The aim of the current study was to investigate the opinions of CFS sufferers themselves, regarding diagnosis and treatment, and compare them to the current thinking of GPs from a different Health Authority but within the same geographical region. We could then address the question of whether the situation had changed in the light of two important reports being in the public domain, namely those by the Royal Colleges [8] and the National Task Force on CFS/ME [1]. Information from the study could then be used to develop educational literature for both GPs and patients regarding CFS diagnosis and management.
Methods
Ethical approval for this study was granted by the Gwent Health Authority. All data were coded to ensure the anonymity of both the patients and the GP Surgeries taking part.

Design
The study took the form of a simple survey proforma and the questions designed as a preliminary point of reference for the production of educational literature for patient and GPs.

Participants
Patient sample
Patient recruitment was from an existing research panel. All of these volunteers had been diagnosed using the Centre for Disease Control (CDC) criteria for CFS [9] at a specialised outpatient clinic some years previously. 197 CFS sufferers were surveyed by postal questionnaire.

Primary care sample
120 questionnaire booklets were distributed by members of staff at the Gwent Health Authority Headquarters into the official postbags for the area’s GP practices.

Neither the GPs nor patients were sent reminders to return the booklets following the first mail shot.

Procedures
Questionnaires
Two short booklets were compiled, by the authors, to glean us much comparable data between the patients and GPs as possible. The booklets compiled for the GPs were done so in as concise a manner as possible in order to maximise response rates in a profession where time is limited. Patient booklets elicited similar information in order to establish comparability with the GP sample. However, patients were also required to comment on any therapy they might have received and their current state of health. In this way it was hoped that data collected from the research panel regarding past diagnosis and management could be compared to the up-to-date information given by the GPs. In this way we would be collecting data relative to our research based on work from previous studies [6].

Patient questionnaires
First and most importantly, the patients were asked if they were still suffering from CFS, and for how long the condition had presented itself. The questionnaire then went on to illicit information regarding the level of primary healthcare received. This included the diagnostic tests and treatment options offered. Patients were also asked if any of the management/treatments offered were successful and asked to rate their health status using a previously validated current state of health measure [10]. This measure assesses the severity of their illness on a 5–item scale ranging from ‘worse than at any stage’ to ‘almost completely recovered’.

GP questionnaire
The GPs surveyed were asked two fundamental questions: (a) did they believe that there was a single entity called Chronic Fatigue Syndrome (often known as Myalgic Encephalomyelitis), and, if so, (b) had they ever diagnosed patients with this illness. If the respondent answered ‘yes’ to both of the above questions they were asked to return the survey. GPs who answered ‘yes’ were then asked to supply details of diagnostic criteria [9,11] and management regimes offered to their patients. They were also asked if their surgery carried any information booklets for patients and if so their source.

Both patients and GPs were asked if they would be prepared to comment on literature complied by healthcare professionals in the future.

Data analysis
Descriptive statistics were performed on the categorical and continuous data. Open-ended questions were collated and categorised.

Results
92 patient questionnaires were completed and returned giving a 48% response rate. A further 21 were returned to sender leaving 84 unaccounted for. Of the questionnaires distributed to the GPs, 45 were returned, two of which were blank giving a 39% response rate.

Patient survey
Of the 92 patient respondents, 78 reported that they were still suffering from CFS (84.8%), indicating a 15.2% recovery rate for the sample. The mean illness duration for the group was 13.14 years (range = 3 to 32 years, s.e.m = 0.63). When asked to rate their current state of health, 2.2% of the sample reported feeling ‘worse than at any stage’ of their illness, 16.3% reported feeling ‘bad’, 32.6% were feeling ‘bad with some recovery’, and 33.7% were ‘recovering with occasional relapses’.

51.6% of the sample indicated that their GP had diagnosed their condition, taking on average 6.58 (range = 2 to 20 appointments, s.e.m = 0.78) appointments to do so. When asked if the patient believed that they were suffering from CFS before their GP’s diagnosis, 52.6% stated that this was the case. The patients were then asked to whom they had turned to for information on CFS (other than their GPs). The majority of respondents (52.2%) had contacted the ME Association. However, 63% stated that they had gained information from ‘other sources’. These
The remaining two patients did not offer a response to the question. 77.2% of the survey respondents had tried 'alternative' therapies to alleviate their symptoms spending on average £981. One respondent reported spending as much as £7000 on alternative therapies.

Finally, 89% of the patients sampled said that they would be willing to comment on information booklets aimed at CFS diagnosis and treatment.

**GP survey**

Of the 45 GP respondents, 55.8% believed that the condition called CFS existed and 67.4% of these had diagnosed patients with CFS. On average, 6.2 (s.e.m = 0.97) separate appointments were required to diagnose the condition. None of the GPs who completed the survey used the CDC or Oxford criteria for CFS, preferring to either conduct investigative tests to rule out other illness (68.8%) and/or refer the patient on to tertiary care (65.6%).

When considering the sub-group of GPs who reported diagnosing CFS, 89.3% offered treatment strategies to the patient. None of the GP surgeries had trained nurses, occupational therapists or physiotherapists capable of offering support, advice or treatment to sufferers in the primary care setting. They also reported being unaware if any such services were presently available in their locality. The most common form of treatment offered by the GPs who responded to the survey was antidepressant therapy. 84% of GPs prescribed Selective Serotonin Re-uptake Inhibitors (SSRI) antidepressants, 28% preferring Serotonin/Noradrenaline Re-uptake Inhibitors (SNRI) and 24% prescribing the Tricyclic and related antidepressants.

Only 14.8% of the surgeries surveyed carried information leaflets on CFS. Most of the literature, it was reported, was supplied by the ME Association.

In terms of referrals to tertiary care, 56.7% of the GPs surveyed were aware that there was a consultant in the area who specialised in CFS. 16.7% referred patients to General Medical out-patients clinics, 6.7% to Rheumatology clinics, 6.7% to Neurology clinics and 6.7% referred patients to Psychological Medicine.

54.5% of the GP respondents were prepared to answer a more detailed questionnaire at a future date and 42.4% were willing to comment on the information leaflets referred to previously.

**Discussion**

This paper aims to describe the current thinking of GPs from a single health authority in Wales. The data was collected as part of an ongoing project which included, amongst others, the need highlight whether GPs were
being made aware of up-to-date information on CFS centres of excellence, its diagnosis and management. If not, our aim was to rectify this by offering to provide GP surgeries with information compiled by healthcare professionals in the field of CFS research.

It is acknowledged that the response rates, by both patients and GPs, for the current survey may appear to be low. However, a recent survey of members of local ME groups (supported by Action for ME and the ME Association) recorded patient response rates of 47% [12]. Furthermore, a ten-centre survey [5] reported GP response rates ranging from 35% to 55%. The latter is in sharp contrast to data presented recently by Bowen et al. [13] indicating a 77% GP response rate to their CFS survey. The data from this survey, however, was collected from GP surgeries served by medical laboratories within their region which may have acted as an incentive to respond. In addition to the differences in the method of sampling, data indicating initial response rates are not recorded; only those from the post-follow-up. With this in mind, the response rates of 48% for patients and 39% for the GPs in the present study seem more indicative of the types of group sampled. We can, therefore, put forward the view that the data reported here does represent an accurate portrayal of patient and GP opinions as long as it is discussed in relation to the situation within Wales and not to the UK as a whole. To further support this, data from the patient research panel group includes respondents who have recovered from Chronic Fatigue Syndrome (CFS). The current state of health measure also indicates that the health status of the group follows a similar profile to that of patients from previous studies (Thomas and Smith, in preparation). Likewise, the GP respondents are split approximately fifty-fifty between those who believe that the condition called CFS exists and those who do not. Therefore, no bias on the basis of patient 'wellness' or GP 'belief' in CFS is indicated here.

Scepticism on the part of GPs in recognising that CFS actually exists remains a problem to this day. Only 56% of the GP responders believe that CFS is a recognised condition despite findings from reports by the joint Royal Colleges and the National Task Force being in the public domain. Of the 44% who did believe that the illness exists, none reported using the CDC or Oxford criteria for CFS definition. This is surprising as both case definitions are readily available to medical and research staff and patient groups alike.

When questioned, only 57% of the GPs surveyed were aware that a CFS specialist was consulting within their local health authority region. The majority of those who were not aware of this referred patients to general medical outpatient clinics. This has been problematical in the past.

Unless the patient is fortunate enough to be referred to a physician who, if not knowledgeable on the subject, is aware of specialist help, this will invariably result in the patient being told that there is 'nothing physically wrong with them'. The patient then returns to a GP who has two courses of action open to them: refer the patient to another outpatient department or try to manage the patient's condition themselves. This is bound to result in frustration on the part of the physician, who has the patient's best welfare at heart, as much as the patient.

Comparisons between the patients who had received a diagnosis from their GP and the GPs, who reported diagnosing CFS, both indicate that the process took approximately 6 appointments. Interestingly, the range of 2 to 20 appointments to diagnose the condition is identical for both groups. It is important during the process of diagnosing CFS, that other illnesses presenting fatigue-like symptoms are ruled out. However, only two-thirds of the GP respondents reported conducting further investigations to exclude these conditions.

It is encouraging to note that more GPs are currently offering treatment strategies compared to the past (89% and 60% respectively). However, antidepressants remain the preferred mode of treatment. Antidepressant therapy does have its role to play in treatment strategies in certain circumstances as described previously (Thomas and Smith, in preparation). But reports by CFS patients of heightened sensitivity to such medication have been widely documented and antidepressants should be prescribed with caution. In addition, findings from successful treatment trials of CBT and GET for the treatment of CFS do not seem to have filtered through to primary healthcare.

The authors acknowledge that General Practitioners' time and resources are limited and that being able to keep up with advances in research is a luxury they can ill-afford. Following the report to the Chief Medical Officer, the Medical Research Council recently set aside a considerable sum of money to support CFS research projects and subsequent information dissemination within the UK. Unfortunately, none of the funding found its way to projects in Wales. This means that the Principality currently trails behind the rest of the country in terms of resources available for research in this area. Due to this short-fall in Welsh funding, it is not surprising that the GPs represented in our survey lack confidence when dealing with patients with CFS.

On a positive note, almost half of the GPs surveyed would welcome helpful, practical advice written by healthcare professionals when dealing with patients whom they suspect may have CFS. However, the state of affairs with regard to the past experiences of the research panel
patients and the current opinions of the GP respondents is all too familiar.

Conclusion
The proposed next step is to produce informative material for both GPs and patients. This material needs to be compiled in conjunction with CFS specialists and will include details of centres of excellence, diagnosis and management.

Abbreviations
CBT - Cognitive Behaviour Therapy
GET - Graded Exercise Therapy
CFS - Chronic Fatigue Syndrome
CDC - Centre for Disease Control and Prevention
GP - General Practitioner
IBS - Irritable Bowel Syndrome
OT - Occupational Therapy
SNRI - Serotonin/Noradrenalin Re-uptake Inhibitor
SSRI - Selective Serotonin Re-uptake Inhibitors

Competing interests
The author(s) declare that they have no competing interest.

Authors' contributions
MAT study design, recruitment of participants, collation of databases, data analysis and manuscript preparation.
APS advice on study design and manuscript.

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An evaluation of counselling and rehabilitation courses for Chronic Fatigue Syndrome

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Abstract

The aim of the current study was to evaluate the services offered by Action for ME to sufferers of Chronic Fatigue Syndrome using measures developed and validated in previous research. Preliminary studies had suggested that clients attending rehabilitation residential courses were benefiting from the service. A further, more in-depth evaluation process with a greater number of health-related outcome measures was warranted. In addition, assessment was widened to include other services offered to sufferers of the illness. Data relating to the usefulness and success of the services (rated by the clients) were also collected. Data from client volunteers were collected at baseline (that is, before intervention) and approximately six months later. Quantitative comparative analyses were conducted using within-group comparisons to assess any improvements in scores at six-month follow-up from baseline. Fifty-six participants completed wide-ranging questionnaires assessing illness history, psychopathology, psychosocial factors and health and well-being. Data relating to improvements in illness status and acceptability of treatment were also collected by means of global outcome measures. Both the counselling and residential groups showed improvements in many areas assessed at follow-up. Most importantly, improvements were indicated in areas such as fatigue and the levels of disability suffered by patients. In addition, there were significant improvements in ratings of mood, anxiety, depression and physical symptoms. Overall, clients reported satisfaction with the care received and most found the services useful. All of the participants who completed the evaluation stated that they would recommend Action for ME services to fellow sufferers. The outcome of the current study is encouraging. The data presented provides evidence of the high level of support and advice Action for ME offers to sufferers of this illness. Furthermore, measurable improvements in scores relating to illness status were accompanied by improvements in mental health and psychosocial variables in the patient group.

Keywords: Chronic fatigue syndrome, action for ME, residential rehabilitation courses, counselling services

Two of the working case definitions for Chronic Fatigue Syndrome (CFS), namely the Oxford (Sharpe et al., 1991) and Centre for Disease Control (CDC) (Fukuda et al., 1994) criteria, characterise the illness as ‘persistent, debilitating fatigue that is not the result of ongoing exertion and is unresolved by rest’. The illness produces a marked reduction in activity, an increase in mental fatigue and other ancillary symptoms such as pain and sleep disturbance (Fukuda et al., 1994). These symptoms can be very debilitating and persistent (Andersen et al., 2004) with little spontaneous recovery (Joyce et al., 1997). Although research into CFS has been rigorous, the illness continues to confound the medical profession. This is primarily because of the cause of the illness and the pathophysiology that maintain it are unknown. For this reason treatments have been investigated on a pragmatic basis.

As the debate surrounding the aetiology of CFS grew, the Royal Colleges of Physicians, Psychiatrists and General Practitioners drafted a report that attempted to document the position from the medical profession’s perspective at that time (Royal Colleges of Physicians, Psychiatrists and General Practitioners, 1996). The Royal Colleges were also involved in the compilation of a report commissioned by the Chief Medical Officer (CMO) in 2002. This document represented not only the views of the medical profession but also patients and support organisations, and addressed issues ranging from nomenclature to possible treatment protocols (CFS/ME Working Group, 2002). Points of particular interest arising from the Working Groups report included: (1) the need for increased awareness of the illness by healthcare professionals, (2) further wide-ranging research studies and (3) better provision for patients in terms of primary, secondary and tertiary healthcare.

These central themes also formed the basis of recommendations made by the National Task Force on CFS/Post Viral Fatigue Syndrome (PVFS)/Myalgic Encephalomyelitis (ME) in 1994 (National Task Force, 1994). The task force was set up at the behest of the Department of Health who had been asked by patient organisations to provide clear guidelines regarding
What does this study explore?

- The services offered by Action for ME to suffers of Chronic Fatigue Syndrome using measures developed and validated in previous research

the diagnosis and management of CFS. Representatives from the registered charity Westcare UK, acting on behalf of CFS sufferers, played a pivotal role in the resulting task force. In addition, the charity was also represented at the CMO Working Group Committee alongside other support groups such as Action for ME (AfME).

Action for ME and Westcare UK recently merged to form an even larger organisation (Action for ME) that continues in its commitment to provide much needed support to and a singular voice for sufferers of CFS. The charity not only produces educational leaflets and booklets containing valuable advice from healthcare professionals and fellow sufferers but also acts with a more hands-on approach in areas such as illness awareness, treatment and management. Medical services, occupational therapy, telephone and face-to-face counselling and residential rehabilitation courses are all options offered by this organisation to its clients. The primary aim of these services is to offer individual clients’ coping strategies for their illness, which include techniques for balancing the levels of activity and rest (that is, pacing).

The long-term effectiveness of one of these services, the residential rehabilitation courses, had been demonstrated in a preliminary investigation conducted in-house (Harrison et al., 2002). A retrospective survey of 12-month follow-up data suggested that 89% of the residential clients rated the courses as ‘very useful’. More importantly, analyses of Profile of Fatigue-Related Symptoms (PFRS) scores (Ray et al., 1993) had indicated that levels of fatigue were significantly improved at follow-up. Emotional distress scores (again using the PFRS scale) were also significantly reduced at twelve-month follow-up. There also appeared to be a trend towards a reduction in somatic symptoms and cognitive difficulties reported by this group of sufferers but these effects did not reach significance. However, the overall success of this small study prompted the call for a more in-depth, independent assessment of the rehabilitation courses.

In contrast to these findings, other centres had produced findings to suggest that Cognitive Behaviour Therapy (CBT) was the most consistently effective form of treatment for CFS (Deale et al., 1997; Sharpe et al., 1996). The rationale behind the effectiveness of CBT seemed to be its capacity to reinforce positive behaviour patterns whilst restructuring dysfunctional beliefs, thoughts and behaviours. In this way the behavioural, cognitive, emotional, physiological and social factors that are thought to prolong the illness are addressed (Surway et al., 1995). However, a recent study comparing the efficacy of CBT and counselling for patients with CFS in primary care produced evidence that both management strategies were equally effective (Ridsdale et al., 2001).

Objectives

In previous studies using data collected from over 300 CFS patients, we produced valid clinical guidelines for CFS based on the principles of evidence-based medicine. Furthermore, a strategy for evaluating healthcare services for CFS had been developed by documenting the characteristics of the patients who were associated with successful outcomes (submitted). A similar approach could be used to evaluate the efficacy of therapies for CFS. Indeed, a study of ours was in progress that aimed to evaluate a combination therapy for CFS using these measures (Thomas et al., 2006; in press).

With assessment protocols in place, the aims of the current study were three-fold: (1) to reproduce the initial positive findings from the previous retrospective study (Harrison et al., 2002), (2) to elaborate on these findings by adding the more formal evaluation tools developed in previous studies (Deale et al., 1997; Smith et al., 1996; Thomas et al., 2006; in press) and (3) to widen the scope of the evaluation to include all the services offered by AfME to their CFS clients.

Methods

Design

Within-group comparisons were used to assess improvements in scores at six-month follow-up from the baseline measures.

Participants

Ethical approval for the research was granted by the host University’s Departmental Ethics Committee. Participants gave informed consent and all data were coded to maintain anonymity.

Chronic Fatigue Syndrome sufferers were recruited through AfME. Potential clients contacting AfME for advice or support were informed of our involvement in service evaluation and asked to volunteer for the research study. Clients were also made aware that participation was voluntary and independent from AfME services. We did not collect data from clients declining our call for their participation as AfME wished to protect client confidentiality in this matter.

Materials

A comprehensive range of subjective measures, used in previous studies to chart the nature of the illness (see Smith et al., 1996 for details), were packaged in the form of two booklets and administered by:

(1) AfME before uptake of services (baseline) and
(2) the research unit six months later. The demographic section of the questionnaire, as well as collecting data relating to gender, age, social status and educational background, required the participant to provide a brief history of their illness. This included illness length, current health status and a twenty-eight-item symptom checklist that, when summed, provided a total symptom score. In addition, data were collected using measures specifically designed to assess the symptoms associated with CFS such as fatigue (Chalder et al., 1993) and fatigue-related symptoms (Ray et al., 1993) as well as measures developed to assess more generalised illness conditions (Cohen & Hoberman, 1983). Low positive mood and high negative mood are also associated with this illness as is abnormal cognition; we therefore included questionnaires that subjectively measure these traits in our evaluation process (Broaderbent et al., 1982; Zevon & Tellegen, 1982). Similarly, CFS is often accompanied by co-morbid anxiety and/or depression; validated measures of psychopathology were consequently incorporated into the questionnaire booklets (Beck et al., 1961; Radloff, 1977; Spielberger et al., 1971; Zigmond & Snith, 1983). Psychosocial factors, such as stress, are believed to exacerbate symptoms and often prolong the illness; for this reason we measured perceived stress in the client groups (Cohen et al., 1983).

A similar set of questionnaires were completed six months later to assess any changes in the client groups. In addition, a set of self-rated global outcome measures, designed to assess fatigue, disability, overall improvement in illness condition and treatment acceptability, were administered. Ratings of overall improvement in illness condition and changes in fatigue and disability were recorded on Likert-type scales (Deale et al., 1997). Each scale ran from extreme negative through ‘no change’ to extreme positive responses. Clients also rated the usefulness and their satisfaction with the treatment (again on Likert-type scales) and were also asked if they would recommend AFME services to other CFS sufferers.

In the case of the residential clients only, a shortened questionnaire was completed at the end of the seven-day programme to assess the clients' immediate reactions to the course. This included levels of fatigue, mood states, psychopathology and global outcome measures.

Procedures

Recruitment took the form of an introductory letter containing details of the nature of the research, a telephone contact for further information (if required) and how to proceed if a participant wished to take part in the evaluation. These were included with the standard information pack sent out by AFME to prospective clients. On receipt of a positive response, the two questionnaire booklets, a consent form, information sheet and covering letter were returned to the client together with a Freepost envelope. The questionnaires administered were completed by the patient at home in their own time, thus minimising the possibility of questionnaire fatigue. A shortened questionnaire was administered to participants attending the residential course just prior to their leaving.

Similar booklets were sent to all clients again six months later, together with a set of global outcome measures (Deale et al., 1997). At this time details of the type and duration of services used were recorded.

Counselling services

The counselling sessions offered by AFME present clients with the opportunity to validate their experience of the illness. During the sessions, sufferers discussed the implications of their illness and were helped to find a meaningful way of life within their present situation. Counselors not only assisted clients understanding of techniques for good management of the illness (including balancing activity and rest [pacing]) but also explored avenues of treatment and care. Emotional aspects of the illness were also explored during these sessions. In addition, carers of CFS sufferers were encouraged to attend counselling sessions with the client. The number of sessions attended was decided by counsellor and client by mutual consent as the therapy progressed.

Residential courses

The residential courses offer a self-management approach to CFS that provides information on how to manage day-to-day living and improve functional ability. It was first developed in the 1990's by recognised experts in CFS, drawing on the conclusions of the 1994 Task Force Report (National Task Force, 1994). The main principles of the course were also supported by the CMO Working Group Report (CFS/ME Working Group, 2002). The courses (usually) run for seven consecutive days with no more than eight clients per course. Group and individual sessions were run for three hours each day led by a team of professional therapists with extensive experience of working with CFS. The team consists of counsellors, occupational therapists (OTs), a general practitioner and a nutritionist and, therefore, offers a combined approach to managing CFS.

The OT helps the client to look at the relationship between activity, rest and symptoms and a balance between these was then found to help stabilise the condition. The first session with the OT involved describing a typical day’s activity. This in turn led to a discussion about how daily activities subsequently affected the condition. The outcome of the discussion was used as an aid to drawing up a pacing programme. In addition, the course provided information regarding sleep hygiene, pain, anxiety and depression. Psychological support, in terms of illness impact on social, personal and emotional areas of the client's lives, were also addressed. The counsellors, physician and
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nutritionist attend the therapy sessions to answer more specific questions within their area of expertise and are also on hand to give advice on a one-to-one basis.

Both the counselling and rehabilitation services assessed in the current study were designed and delivered by trained specialists in accordance with guidelines produced by the National Task Force and the CFS/ME Working Group. Each healthcare professional was trained in-house to specifically address the problems and concerns experienced by patients with CFS and their carers.

Data analysis

Categoric data were analysed using Chi-squared cross-tabulation. Continuous data were analysed using analyses of variance (ANOVA) to compare the intervention groups at baseline. Paired-sample t-tests were used to assess within group differences at follow-up.

Results

The Chronic Fatigue Syndrome client sample

Seventy-five AfME clients completed the baseline questionnaire measures. Fifty-six of these went on to complete the full evaluation process. In all, four intervention groups were recruited; (1) OT clients \(n=5\), (2) telephone counselling clients \(n=6\), (3) residential course clients \(n=21\) and (4) counselling clients \(n=24\). We do not have information relating to the service uptake of the 18 clients who did not complete the evaluation as these data were collected at the six-month follow-up point. We did, however, compare the baseline demographics of these non-completers to the 56 participating clients. Table 1 compares these two groups.

There were no significant differences between the age, gender, marital status, educational status, health status or illness length of those who completed the evaluation and those who did not. However, the non-completers recorded significantly higher total symptom scores at baseline.

Insufficient numbers were recruited from the telephone counselling and occupational therapy groups for detailed analyses, therefore the results section will concentrate on the residential and counselling client groups. Table 2 represents demographic and illness history data for the two intervention groups.

One-way analysis of variance (ANOVA) and Chi-squared cross-tabulation showed that there were no significant differences between the groups at baseline for any of measures used. The exception to this being the age and gender of the participants in the two groups; the counselling clients mean age was significantly lower than that of the residential clients (counselling mean age = 39; residential mean age = 48.6; \(F(1, 43) = 7.651; p < 0.008\)) and the counselling group also differed in terms of gender ratio; there were approximately equal numbers of male and female clients in this group \(\chi^2 = 4.09; df = 1; p < 0.044\). These differences were addressed by means of within-group analyses.

Residential course

Clients attending the residential courses were asked to complete a shortened questionnaire to assess their status as soon as the course ended. Table 3 presents the data collected at this time point that were analysed using a paired-sample t-test.

| Table 1. Baseline demographics and illness history data for those clients who completed the evaluation and those who did not. |
|---|---|---|
| Clients completing evaluation \(n=56\) | Clients not completing evaluation \(n=19\) |
| Gender (%) | | |
| Male | 28.6 | 15.8 |
| Female | 71.4 | 84.2 |
| Mean age (s.e.m.) | 41.6 | 37.9 |
| (1.8) | (2.9) |
| Marital status (%) | | |
| Married | 46.4 | 31.6 |
| Education (%) | | |
| BSc or BA | 34.5 | 31.6 |
| Current state of health (%) | | |
| Worse than at any stage | 16.1 | 5.3 |
| Bad | 23.2 | 15.8 |
| Bad with some recovery | 30.4 | 52.6 |
| Recovering with occasional relapses | 28.6 | 21.1 |
| Almost completely recovered | 1.8 | 5.3 |
| Mean illness length—months (s.e.m.) | 82.1 | 53.6 |
| (11.6) | (9.1) |
| Total symptom scores (s.e.m.) | 13.7 | 16.8* |
| (0.7) | (1.5) |

*\(F(1, 73) = 4.121; p < 0.05\).
These data indicate that clients report significantly lower physical and mental fatigue scores post-residential course when compared to the baseline scores. They also reported significantly higher positive mood scores and significantly lower negative mood scores post-residential course. In addition, clients in this group reported significantly lower levels of depression, anxiety and emotional distress (PFRS) after completing the course.

Improvements within this group were sustained and further increased at the six-month follow-up point (see Table 4).

Clients continued to show the improvements in physical and mental fatigue reported post-residential course. Similarly, they reported lower negative mood scores, depression, anxiety and emotional distress scores. In addition, these clients reported improvements in fatigue, cognitive difficulties and somatic symptom scores (PFRS) and lower perceived stress and general anxiety scores. The general and mental health scores of this group were also improved as was their level of physical symptoms. There was also a significant decrease in the impact fatigue had on the individual when rating it as a life-changing problem.

Table 3. Residential client questionnaire scores immediately post-course (paired-sample t-test).

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline score</th>
<th>Post-course score</th>
<th>t, df, p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical fatigue</td>
<td>20.05</td>
<td>12.95</td>
<td>5.203; 18; &lt;0.000</td>
</tr>
<tr>
<td>(low scores = low physical fatigue)</td>
<td>(0.75)</td>
<td>(1.40)</td>
<td></td>
</tr>
<tr>
<td>Mental fatigue</td>
<td>13.28</td>
<td>8.56</td>
<td>3.879; 17; &lt;0.001</td>
</tr>
<tr>
<td>(low scores = low mental fatigue)</td>
<td>(0.89)</td>
<td>(1.03)</td>
<td></td>
</tr>
<tr>
<td>Positive mood</td>
<td>25.22</td>
<td>35.33</td>
<td>-3.521; 17; &lt;0.003</td>
</tr>
<tr>
<td>(high scores = more positive mood)</td>
<td>(2.64)</td>
<td>(2.65)</td>
<td></td>
</tr>
<tr>
<td>Negative mood</td>
<td>30.47</td>
<td>22.47</td>
<td>3.151; 18; &lt;0.006</td>
</tr>
<tr>
<td>(low scores = lower negative mood)</td>
<td>(2.67)</td>
<td>(2.25)</td>
<td></td>
</tr>
<tr>
<td>Depression (CES)</td>
<td>49.33</td>
<td>37.22</td>
<td>3.621; 17; &lt;0.002</td>
</tr>
<tr>
<td>(high scores = greater depression)</td>
<td>(2.73)</td>
<td>(2.51)</td>
<td></td>
</tr>
<tr>
<td>State anxiety</td>
<td>48.84</td>
<td>39.68</td>
<td>2.704; 18; &lt;0.015</td>
</tr>
<tr>
<td>(low scores = lower anxiety levels)</td>
<td>(3.21)</td>
<td>(2.37)</td>
<td></td>
</tr>
<tr>
<td>Emotional distress: PFRS</td>
<td>58.58</td>
<td>43.00</td>
<td>2.871; 18; &lt;0.010</td>
</tr>
<tr>
<td>(high scores = greater emotional distress)</td>
<td>(5.33)</td>
<td>(4.66)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Scores are the group means with standard error of the mean (s.e.m) in parenthesis.


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What does this study tell us?
- Both the counselling and residential groups showed improvements in areas such as fatigue and the levels of disability suffered by patients
- There were significant improvements in ratings of mood, anxiety, depression and physical symptoms
- Clients reported satisfaction with the care received and most found the services useful

Counselling clients
The counselling clients provided a similar profile of improvement at six-month follow-up (see Table 5). Again there were improvements in physical and mental fatigue and mental and general health scores (MOS). They also reported significantly improved positive and negative mood, scores, depression and anxiety scores. Similarly, the data indicated that the fatigue, somatic symptom and emotional distress scores (PFRS) of these sufferers were also significantly improved. The counselling clients also reported significantly lower physical symptom and perceived stress scores at follow-up.

Table 4. Residential client questionnaire scores at follow-up (paired-sample t-test).

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline score</th>
<th>Follow-up score</th>
<th>t, df, p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOS SF36:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>55.43</td>
<td>65.71</td>
<td>-2.354; 20; &lt;0.029</td>
</tr>
<tr>
<td>(low scores = low mental health rating)</td>
<td>(5.05)</td>
<td>(4.40)</td>
<td></td>
</tr>
<tr>
<td>General health</td>
<td>28.62</td>
<td>42.71</td>
<td>-3.608; 20; &lt;0.002</td>
</tr>
<tr>
<td>(low scores = low general health rating)</td>
<td>(4.01)</td>
<td>(4.77)</td>
<td></td>
</tr>
<tr>
<td>Physical fatigue</td>
<td>20.29</td>
<td>13.90</td>
<td>5.379; 20; &lt;0.000</td>
</tr>
<tr>
<td>(low scores = low physical fatigue)</td>
<td>(0.71)</td>
<td>(1.18)</td>
<td></td>
</tr>
<tr>
<td>Mental fatigue</td>
<td>13.35</td>
<td>10.80</td>
<td>3.243; 19; &lt;0.004</td>
</tr>
<tr>
<td>(low scores = low mental fatigue)</td>
<td>(0.63)</td>
<td>(0.89)</td>
<td></td>
</tr>
<tr>
<td>Fatigue Problem Rating scale</td>
<td>6.20</td>
<td>5.40</td>
<td>2.223; 19; &lt;0.039</td>
</tr>
<tr>
<td>(low scores = fatigue less of a problem)</td>
<td>(0.34)</td>
<td>(0.47)</td>
<td></td>
</tr>
<tr>
<td>HAD: Anxiety</td>
<td>10.00</td>
<td>7.71</td>
<td>2.892; 20; &lt;0.009</td>
</tr>
<tr>
<td>(low scores = lower anxiety levels)</td>
<td>(1.12)</td>
<td>(0.88)</td>
<td></td>
</tr>
<tr>
<td>Negative mood</td>
<td>29.45</td>
<td>20.36</td>
<td>4.661; 21; &lt;0.000</td>
</tr>
<tr>
<td>(low scores = lower negative mood)</td>
<td>(2.41)</td>
<td>(2.00)</td>
<td></td>
</tr>
<tr>
<td>Depression (CES)</td>
<td>47.57</td>
<td>39.00</td>
<td>3.165; 20; &lt;0.005</td>
</tr>
<tr>
<td>(high scores = greater depression)</td>
<td>(2.57)</td>
<td>(2.83)</td>
<td></td>
</tr>
<tr>
<td>PFRS:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional distress</td>
<td>55.09</td>
<td>39.28</td>
<td>3.146; 20; &lt;0.005</td>
</tr>
<tr>
<td>(high scores = greater emotional distress)</td>
<td>(4.79)</td>
<td>(4.32)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>66.00</td>
<td>53.50</td>
<td>3.273; 21; &lt;0.004</td>
</tr>
<tr>
<td>(high scores = greater fatigue levels)</td>
<td>(2.82)</td>
<td>(3.53)</td>
<td></td>
</tr>
<tr>
<td>Cognitive difficulties</td>
<td>50.18</td>
<td>41.45</td>
<td>2.463; 21; &lt;0.023</td>
</tr>
<tr>
<td>(high scores = more cognitive difficulties)</td>
<td>(3.63)</td>
<td>(3.40)</td>
<td></td>
</tr>
<tr>
<td>Somatic symptoms</td>
<td>56.57</td>
<td>46.62</td>
<td>2.115; 20; &lt;0.047</td>
</tr>
<tr>
<td>(high scores = more somatic symptoms)</td>
<td>(4.19)</td>
<td>(3.38)</td>
<td></td>
</tr>
<tr>
<td>Trait anxiety</td>
<td>52.62</td>
<td>46.19</td>
<td>3.109; 20; &lt;0.006</td>
</tr>
<tr>
<td>(low scores = lower anxiety levels)</td>
<td>(2.78)</td>
<td>(2.96)</td>
<td></td>
</tr>
<tr>
<td>Physical symptoms</td>
<td>23.95</td>
<td>20.24</td>
<td>2.610; 20; &lt;0.017</td>
</tr>
<tr>
<td>(low scores = lower physical symptoms)</td>
<td>(1.75)</td>
<td>(1.68)</td>
<td></td>
</tr>
<tr>
<td>Perceived stress</td>
<td>30.20</td>
<td>26.60</td>
<td>2.882; 19; &lt;0.010</td>
</tr>
<tr>
<td>(low scores = lower perceived stress)</td>
<td>(1.55)</td>
<td>(1.68)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Scores are the group means with S.E.M in parenthesis.

1Ware & Sherbourne, 1992.
2Marks, 1988.

Global outcome measures
When asked to rate overall improvement in their condition at six-month follow-up, 83% of the counselling clients and 66% of the residential clients reported that they were 'better' or 'very much better'. Of those attending counselling, 67% reported that their level of fatigue was 'better' or 'much better' and 75% reported lower levels of disability. In those attending the residential course these figures were 62% and 57% respectively. In terms of acceptability of the treatments, 96% of the counselling clients and 95% of the residential clients were 'satisfied' or 'very satisfied' with the service received from AfME and 79% (counselling) and 86% (residential) found the service 'useful' or 'very useful'. Finally, all of the clients who completed the assessment procedure said that they would recommend the services provided by AfME to other CFS sufferers.

Discussion
This study aimed to document the efficacy of management strategies offered to sufferers of CFS by AfME. Retrospective data collected from clients attending one of the services offered by AfME,
Table 5. Counselling client’s questionnaire scores at follow-up (t-test).

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline score</th>
<th>Follow-up score</th>
<th>t, df, p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOS SF36:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>55.48</td>
<td>66.26</td>
<td>-2.908; 22; &lt;0.008</td>
</tr>
<tr>
<td>(low scores = low mental health rating)</td>
<td>(3.11)</td>
<td>(3.78)</td>
<td></td>
</tr>
<tr>
<td>General health</td>
<td>24.54</td>
<td>30.58</td>
<td>-2.204; 23; &lt;0.031</td>
</tr>
<tr>
<td>(low scores = low general health rating)</td>
<td>(2.99)</td>
<td>(2.97)</td>
<td></td>
</tr>
<tr>
<td>Physical fatigue</td>
<td>19.54</td>
<td>17.08</td>
<td>2.298; 23; &lt;0.031</td>
</tr>
<tr>
<td>(low scores = low physical fatigue)</td>
<td>(0.91)</td>
<td>(1.18)</td>
<td></td>
</tr>
<tr>
<td>Mental fatigue</td>
<td>12.88</td>
<td>11.50</td>
<td>2.253; 23; &lt;0.034</td>
</tr>
<tr>
<td>(low scores = low mental fatigue)</td>
<td>(0.67)</td>
<td>(0.70)</td>
<td></td>
</tr>
<tr>
<td>Fatigue Problem Rating scale</td>
<td>6.54</td>
<td>5.67</td>
<td>2.834; 23; &lt;0.009</td>
</tr>
<tr>
<td>(low scores = fatigue less of a problem)</td>
<td>(0.29)</td>
<td>(0.38)</td>
<td></td>
</tr>
<tr>
<td>HAD:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>9.21</td>
<td>7.92</td>
<td>2.141; 23; &lt;0.043</td>
</tr>
<tr>
<td>(low scores = lower anxiety levels)</td>
<td>(0.86)</td>
<td>(0.92)</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>8.71</td>
<td>7.25</td>
<td>2.376; 23; &lt;0.026</td>
</tr>
<tr>
<td>(high scores = greater depression)</td>
<td>(0.84)</td>
<td>(0.74)</td>
<td></td>
</tr>
<tr>
<td>Positive mood</td>
<td>22.91</td>
<td>30.27</td>
<td>-2.861; 21; &lt;0.009</td>
</tr>
<tr>
<td>(high scores = more positive mood)</td>
<td>(1.71)</td>
<td>(2.22)</td>
<td></td>
</tr>
<tr>
<td>Negative mood</td>
<td>27.95</td>
<td>20.50</td>
<td>3.247; 21; &lt;0.004</td>
</tr>
<tr>
<td>(low scores = lower negative mood)</td>
<td>(2.23)</td>
<td>(2.20)</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>46.18</td>
<td>38.82</td>
<td>3.336; 21; &lt;0.003</td>
</tr>
<tr>
<td>(CES) (high scores = greater depression)</td>
<td>(2.10)</td>
<td>(2.33)</td>
<td></td>
</tr>
<tr>
<td>PFRS:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional distress</td>
<td>51.41</td>
<td>41.59</td>
<td>2.202; 21; &lt;0.039</td>
</tr>
<tr>
<td>(high scores = greater emotional distress)</td>
<td>(4.03)</td>
<td>(4.02)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>61.09</td>
<td>51.00</td>
<td>2.805; 21; &lt;0.011</td>
</tr>
<tr>
<td>(high scores = greater fatigue levels)</td>
<td>(3.10)</td>
<td>(3.77)</td>
<td></td>
</tr>
<tr>
<td>Somatic symptoms</td>
<td>48.82</td>
<td>43.32</td>
<td>2.337; 21; &lt;0.029</td>
</tr>
<tr>
<td>(high scores = more somatic symptoms)</td>
<td>(3.76)</td>
<td>(4.22)</td>
<td></td>
</tr>
<tr>
<td>Depression (BDI)</td>
<td>17.71</td>
<td>14.32</td>
<td>2.622; 21; &lt;0.016</td>
</tr>
<tr>
<td>(high scores = greater depression)</td>
<td>(1.48)</td>
<td>(1.54)</td>
<td></td>
</tr>
<tr>
<td>Trait anxiety</td>
<td>50.08</td>
<td>45.46</td>
<td>2.233; 23; &lt;0.036</td>
</tr>
<tr>
<td>(low scores = lower anxiety levels)</td>
<td>(2.34)</td>
<td>(2.30)</td>
<td></td>
</tr>
<tr>
<td>Physical symptoms</td>
<td>21.74</td>
<td>18.43</td>
<td>2.218; 23; &lt;0.037</td>
</tr>
<tr>
<td>(low scores = lower physical symptoms)</td>
<td>(1.69)</td>
<td>(2.02)</td>
<td></td>
</tr>
<tr>
<td>Perceived stress</td>
<td>28.46</td>
<td>25.08</td>
<td>2.366; 23; &lt;0.027</td>
</tr>
<tr>
<td>(low scores = lower perceived stress)</td>
<td>(1.58)</td>
<td>(1.66)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Scores are the group means with s.e.m. in parenthesis.

namely the residential courses, had indicated that CFS sufferers were benefiting from this approach (Harrison et al., 2002). However, these data were of an exploratory nature and a more formal evaluation, applied independently with pre-intervention data collection, was required.

Assessment for the current study was carried out using methods and measuring instruments developed in earlier studies into the illness (Deale et al., 1997; Smith et al., 1996; Thomas et al., 2006; In press). Clients contacting AfME about their services were asked to participate in an independent evaluation. Data were then collected to provide baseline measures. Data were also collected six months later to assess any differences from the baseline scores and would, therefore, assess the effectiveness of the care received. Residential course clients were also asked to complete a brief questionnaire immediately after the seven-day course.

Of the 75 clients who returned the baseline measures, 56 went on to complete the six-month follow-up evaluation. Comparative analyses of the characteristics for those who did not complete the assessment process and those who did provided evidence to suggest that the non-completers had significantly higher total symptom scores at baseline. One might speculate, therefore, that the severity of their symptoms prevented further participation but we have no way of confirming this. When comparing the baseline characteristics of clients attending the residential courses to clients attending counselling, we found that the counselling group were significantly younger and consisted of equal numbers of men and women. We are unable to offer any explanation for these data other than that of sampling error; the CFS profile suggests that sufferers are predominantly middle-aged married females.

Follow-up data collected from the residential clients immediately after the course, indicate the effectiveness of the service. Although the courses themselves are quite time consuming and physically demanding, participants reported significantly lower mental and physical fatigue scores compared to the baseline measures. Changes in positive and negative affect (post-residential course) together with lower anxiety, depression and emotional distress scores, indicate the
tangible level of support this approach offers to sufferers. More importantly, these benefits are sustained and become more wide-ranging as time passes.

Similarly, positive findings are also observed when considering data from the counselling services. Furthermore, areas of improvement include psychopathology (anxiety and depression) and psychosocial factors (perceived stress), which have been implicated as factors that act in prolonging the illness. In addition, the number and severity of symptoms, both in terms of fatigue and physical symptoms are lower at six-month follow-up when compared to the pre-intervention scores.

These data are also supported by the global outcome measures. Many clients reported feeling ‘better’ or ‘much better’ when asked to assess overall improvement in their condition, levels of fatigue experienced were improved and the level of disability resulting from the illness diminished. Finally, the majority of clients rated the usefulness of the services highly, were satisfied with the level of care provided and would recommend AfME and its services to other CFS sufferers.

We were not able to collect further data on those clients who declined our follow-up call nor did we recruit a control group. We acknowledge these as study limitations. However, overall, the current study does indicate that the services evaluated are of benefit to their clients and that these benefits are measurable. An important consideration for any service providers is that of client satisfaction. Our data suggest that the majority of those assessed were satisfied with the service received and found it useful. An overwhelming endorsement for AfME services is that 100% of the clients questioned would recommend the organisation to fellow sufferers. It is, therefore, important that AfME is able to continue offering its expertise and advice to people with CFS and that this approach is made widely available.

Acknowledgements

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References


Counselling and rehabilitation courses for CFS


3.9 Paper 9
Counselling and Psychotherapy Research, June 2006; 6(2): 91–99

ORIGINAL ARTICLE

The effect of Multi Convergent Therapy on the psychopathology, mood and performance of Chronic Fatigue Syndrome patients: A preliminary study

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1Centre for Occupational and Health Psychology, School of Psychology, Cardiff University, UK and 2MCT Clinic Director, Department of Physiotherapy, University Hospital of Wales, Heath Park, Cardiff, UK

Abstract
Objectives: Multi Convergent Therapy combines approaches such as Cognitive Behaviour Therapy and Graded Exercise Therapy in an holistic treatment of Chronic Fatigue Syndrome. Initial follow-up data showed that patients were benefiting from this individualised form of therapy. The objective of the present study was to evaluate this Multi Convergent approach, developed at a specialised Chronic Fatigue Syndrome Outpatient clinic in Cardiff, and compare it to Relaxation Therapy and control groups using multiple outcome measures.

Design: Thirty-five participants fitting the Centre for Disease Control criteria for Chronic Fatigue Syndrome were recruited from two outpatient clinics and members of our existing patient panel. Patients were assigned to Multi Convergent Therapy (N = 12), Relaxation Therapy (N = 14) or recruited as controls (N = 9).

Methods: Each patient completed a battery of mood and performance tasks along with comprehensive set of questionnaires at baseline, post-treatment and at six-month follow-up. These measures had been validated in previous studies on untreated patients and matched healthy controls.

Results: Patients attending the Multi Convergent Therapy clinic showed statistically significant improvements in many of our measures. Most importantly we have produced data indicating that Multi Convergent Therapy provides improvements in objective measures of psychomotor performance and cognition.

Discussion: The outcomes of this small study are encouraging. Multi Convergent Therapy has not only produced results indicating significant improvements in standardised questionnaire based measures but also in objective cognitive performance tasks. The next step would be to assess Multi Convergent Therapy at the primary medical care level, with a greater number of patients to further evaluate its efficacy as a treatment for Chronic Fatigue Syndrome.

Keywords: Multi Convergent Therapy, relaxation therapy, graded exercise therapy, cognitive behaviour therapy, Chronic Fatigue Syndrome

Introduction
Over the years, Chronic Fatigue Syndrome (CFS), in terms of nomenclature, has been shown to mean different things to different clinicians (The National Task Force on CFS/ME, 1998). The development of a working case definition for Chronic Fatigue Syndrome in 1988 (Holmes et al., 1988) provided a structured method for categorising the illness. Fukuda (and colleagues) developed a further modified definition of CFS in 1994, namely the Centre for Disease Control (CDC) criteria (Fukuda et al., 1994). Here a CFS patient is described as one having suffered from fatigue for at least six months with substantial functional impairment present. New onset is required with four or more co-existing symptoms, where cognitive or neuropsychiatric symptoms may be in evidence.

In terms of CFS prevalence, a review of large surveys by Afari and Buchwald (2003) reported that as many as half the general population reported fatigue-like symptoms (Chen, 1986; Pawlikowska et al., 1994) and 20% of fatigue sufferers sought medical care (Bates et al., 1993; Cathebras et al., 1992; David et al., 1990; Kroenke et al., 1988; McDonald et al., 1993). They also concluded that only a minority of these people experience a level of fatigue that is both debilitating and persistent. However, research has comprehensively shown that this debilitating and persistent fatigue has far-reaching financial consequences in terms of employment status and healthcare resources to say nothing of its impact on quality of life for its sufferers.

The heterogeneous nature of Chronic Fatigue Syndrome has long since been established (Wessley...
What does this study explore?
- How well Multi Convergent Therapy works for sufferers from Chronic Fatigue Syndrome

et al., 1996 for example). Complaints of excessive physical and mental fatigue with varying levels of pain are, to a greater or lesser extent, accompanied by myriad other equally distressing symptoms: anxiety and depression (Farmer et al., 1995), sleep abnormalities (Smith et al., 1996), cognitive and behavioural problems (Smith, 1992; Smith et al., 1993). This can, at primary care level, lead to the most disabling feature presented in each individual case dictating subsequent management strategies. Inevitably numerous hospital referrals to a variety of outpatient clinics follow, resulting in the patient only discovering what is not wrong with them. General Practitioners may then choose to tackle these cases from a fatigue, pain or sleep disturbance perspective. This, more often than not, involves the use of antidepressant therapy to either lift mood (if fatigue is considered to be a result of depressive illness) and/or promote restful sleep. This is not to say that antidepressant therapy does not have a role to play in the alleviation of symptoms associated with CFS (Thomas and Smith, in preparation). It may be the case, however, that the type and dose of antidepressant prescribed along with the extent and timing of their intervention will vary from patient to patient.

When considering the range of abnormalities present in this illness, Surawy et al. (1995) suggested that once CFS had established itself within a patient, cognitive, behavioural, emotional, physiological and social factors might work together to perpetuate it. Also in 1995, Marshall et al. reported evidence from a preliminary study indicating that decision making and motor speed were slower in both choice reaction time and simple reaction time when compared to healthy controls. Smith et al. (1991, 1993) also produced data highlighting differences in sustained attention in this patient group and Marcel et al. (1996) demonstrated both verbal and nonverbal learning and memory impairments. Conclusions drawn by Taillefer et al. (2002) supported the role of depression and illness cognitions in disability of CFS sufferers.

Measurable improvements in the impairments associated with CFS were therefore a desirable outcome for the current research project.

Previous research
We had already conducted a large-scale study charting the natural illness history of over three-hundred Chronic Fatigue Syndrome sufferers over a three year period. Data were collected from patients attending an out-patient clinic specifically set up to research CFS in South Wales. Patients fitting the Centre for Disease Control (CDC) criteria for Chronic Fatigue Syndrome were recruited onto a research panel and evaluated by means of wide-ranging questionnaires designed to assess the possible psychopathological and psychosocial factors associated with the illness. To achieve this, baseline data from the patient group were compared to 126 match controls recruited from the general population (Thomas & Smith, in preparation). Furthermore, both patients and controls completed a battery of objective performance tasks designed to highlight changes in cognition. Some interesting findings from this study were: (a) patients reported similar sleep duration to the controls but were significantly less likely to express satisfaction with their sleep quality. Further to this, patients indicating recovery were found to report more satisfaction with the quality of their sleep. This seemed to imply that sleep abnormalities do play an important role in the exacerbation of symptoms; (b) patients reported significantly more physical symptoms, higher levels of fatigue and more somatic symptoms than the control group. Furthermore, patients recorded higher negative mood scores, state and trait anxiety scores, depression scores, emotional distress and perceived stress scores and lower positive mood scores when compared to the control group, (c) laboratory testing produced data indicating that CFS patients were less alert, had lower hedonic tone scores and were more anxious than the controls. Differences between the CFS and control groups were studied using objective measures of performance such as simple reaction time, sustained attention, episodic and working memory. Psychomotor speed (as measured by a simple reaction time task) was significantly slower in the CFS population. Evidence for psychomotor slowing along with memory and attention deficits in this group appeared to largely reflect sleep disorders and/or physical deconditioning (Smith et al., 1996) and (d) cognitive abnormalities were also highlighted with patients reporting more cognitive failures and cognitive difficulties (Thomas and Smith, in preparation).

Furthermore, initial findings had demonstrated that the psychosocial, psychopathology, mood and performance data could be used as markers to accurately assess a patient’s state of health. Certain measures were demonstrated to be important tools in predicting those individuals who would improve, those who would worsen and those whose condition would not change. In this respect, recovery in this patient group has been examined by considering a current state of health variable (Smith et al., 1996). The patient was asked to rate their health on a five-item scale ranging from ‘worse than at any stage’ to ‘almost completely recovered’. Other measures were observed to be sensitive to current state of health status such as the number of symptoms reported. This led us to surmise that improvements in health status would result in changes in other aspects of the disease such as positive and negative mood. A repeated measure of current state of health at six-month follow-up provided data indicating that 6% of this cohort recovered within this time frame (Thomas
and Smith, in preparation). This recovery rate would, therefore, have to be considered when evaluating the benefits of possible treatments as it is possible that 6% of any CFS sample will recover over a six-month period without intervention.

**Interventions for CFS**

Interventions for CFS can be broadly categorised as behavioural (Cognitive Behavioural Therapy (CBT), Graded Exercise Therapy (GET)) and pharmacological (antidepressants, corticosteroids) with some studies combining these approaches (Morris et al., 1998). Previous research had indicated that two therapies were successful in alleviating the symptoms of the illness, namely, Cognitive Behaviour Therapy (CBT) and Graded Exercise Therapy (GET) (Deale et al., 1997; Fulcher & White, 1997).

In addition, however, organisations such as Action for ME (AFME) have developed rehabilitation courses and counselling services designed specifically for sufferers of CFS. A preliminary retrospective study provided data indicating that clients who attended the rehabilitation courses found the service useful and reported improvements in fatigue levels up to 12 months later (Harrison et al., 2002). Therefore, a further more formal assessment of these courses together with the counselling services offered by AFME was conducted. Initial findings not only replicate previous data but also indicate that counselling is of measurable benefit to people with this illness and that improvements in the condition were maintained over time (Thomas & Smith, in preparation).

The multi-faceted nature of the CFS indicates that any treatment regime would have to reflect this. It was this belief that led to development of an intervention that would produce benefits in several domains.

**Multi Convergent Therapy**

A Multi Convergent Therapy clinic was set up in 1991 to provide a service for patients whose condition did not respond to first line medical intervention and where no solution was readily available. The technique was developed to tackle a wide range of problems namely, tinnitus, vertigo, anxiety, hyperventilation syndrome, irritable bowel syndrome and other functional somatic syndromes as well as CFS (Shaw et al., 1991; Sadlier et al., 1995). Multi Convergent Therapy (MCT) combines aspects of behavioural therapy and fitness training along with, in some cases, pharmacological intervention in an attempt to address the many co-existing clinical features of the condition simultaneously. An added benefit of this multi-dimensional approach was that a single therapist could conduct all components of the technique. Other aspects such as behaviour modification, breathing and relaxation techniques, connective tissue massage and brief focused psychodynamic counselling were combined in a tailored therapy programme.

The approach aimed to re-focus the patient by emphasising mechanisms of internal control and therapy was adapted constantly to reflect the needs of the patient. The number of therapy sessions attended by each patient was not restricted; instead, the requirements of each patient were assessed on a regular basis. Elements were adapted to differences within the presented condition, which proved essential in heterogeneous groups like CFS. The therapeutic approach blends different aspects of MCT; no one patient received exactly the same service as another, instead, they received a slightly different approach. This meant that for certain patients exercise was stressed, with others CBT etc. The patient and therapist would, during this process, work through the following stages: (a) exploration of the predisposing precipitating and perpetuating factors, psychological, physiological and social, (b) exploration of model of illness as well as neuropsychological model of neuroplasticity, (c) introduction of behaviour modification in relation to cognitions, (d) exploration of anxiety/depression (if any existed), (e) identifying positive and negative patterns of behaviour pertaining to fatigue etc., (f) coping strategies, (g) exploration of sleep problems and rectification where problems existed (sleep hygiene) and (h) application of techniques (meditation etc.) regarding behaviour modification. Overall, the technique conforms to the type of individualised therapy programme suggested by the Working Party on CFS/ME, namely a combination of CBT, pacing and GET (the Working Party on CFS/ME, 2001).

In a retrospective study of twenty CFS patients treated by this Multi Convergent method, a statistically significant number of patients reported feeling “better” or “much better” immediately post-therapy (Sadlier et al., 2000). To consolidate these earlier findings it became necessary to formally evaluate the effectiveness of the Multi Convergent approach as an acceptable therapy for CFS.

**Relaxation therapy**

The relaxation treatment procedure used in this study was based on the work of Lars-Goran Ost (1997). The Rapid Relaxation Technique assessed in this paper had not, in the past, been limited to CFS but had been successfully used for a wide range of problems such as tinnitus and pain. Furthermore, the treatment did not claim to cure CFS, but aimed to help patients target specific areas of the illness, thus facilitating symptom relief. Rapid Relaxation, therefore, offered the patient a way of coping with their symptoms and managing them. The therapist would guide the patient through the relaxation technique over a period of ten weeks; each session revising the previous one before moving on to a different major muscle group. Relaxation Therapy had been an approach favoured by various centres and patient groups (Action for ME for example) throughout England, Scotland and Wales and had been used as
a comparison by other research groups (Deale et al., 1997).

The aim of the present study was to evaluate MCT in parallel with Relaxation Therapy and a non-treatment control group. To achieve this, we administered the wide-ranging questionnaire-based measures and cognitive performance tasks used previously to highlight abnormalities between CFS and control groups along with measures adopted by other researchers in the field (Sharpe et al., 1996; Thomas and Smith, in preparation). This paper will discuss the formal assessment of MCT for the treatment of CFS in terms functional measures of performance, and established indicators of quality of life, sleep and psychopathology.

Method

Ethical approval for the research was granted by the appropriate Local Health Authorities and the study registered (ISRCTN31455243). All data were coded to ensure the anonymity of the patient. The researcher collecting these data remained blind to patient group throughout the study.

Design

The study was mixed design with between-subjects factor and a within-subjects factor. Patients were assessed before, during and after therapy to identify areas of improvement within the groups over time as well as reporting whether one group showed greater improvements from their baseline scores compared to the others.

Participants

Recruitment took place at two outpatient clinics and from our existing research panel of CFS sufferers. All of the patients participating in the study had had their condition diagnosed by the same Consulting Physician and gave signed, informed consent. For inclusion into the study participants had to fit the CDC criteria for CFS, be able to attend all of the therapy and assessment sessions and have a Karnofsky performance score of 70% or less (Karnofsky et al., 1948). This implied that functional impairment was such that the patient could not work full or part-time. Forty Chronic Fatigue Syndrome patients were recruited to the study. Of these five withdrew (all in the MCT group); one strongly believed that they were not suffering from CFS, one due to family problems and the remaining three failed to attend their first therapy session. Of the thirty-five remaining participants, twelve were allocated to the MCT group, fourteen into the Relaxation group and nine were recruited as controls.

Procedure

Treatment assignment. Patients recruited into the trial were assigned to a treatment group individually (due to the small numbers in the study). Letters of referral for both the MCT clinic and Relaxation therapist were prepared for each patient volunteer. These were placed in addressed envelopes. Each addressed envelope was then placed into a larger blank envelope. One envelope was then selected blind by a colleague who had no other involvement in the study. The selected blind envelope was then opened, and the letter sent to the appropriate therapist. The un-chosen letter was shredded. The patient was contacted by the chosen therapist to arrange subsequent assessment through a third-party. The control group was recruited separately from the active arms of the study.

Therapy sessions and assessments. Each patient in the treatment groups received approximately ten one-hour sessions on a one-to-one basis. The MCT was conducted by the therapist who developed the technique (MJS) and the Relaxation Therapy was conducted by two male psychologists following a set protocol manual. Patients were assessed at initial clinic visit, the week before intervention, mid way through intervention, immediately post-treatment and six months post-treatment. The controls completed these five assessment sessions based on a ten-week therapy time frame.

Questionnaires. A comprehensive range of measures were administered to the patient at each assessment session (Smith et al., 1996). The demographic section of the questionnaire included a brief illness history profile and a twenty-eight item symptom checklist. A health-related behaviours section of the questionnaire assessed sleeping and eating patterns, social and leisure activities and changes in exercise levels before and after illness onset. Along with ratings of stress, social support and cognitive difficulties we aimed to assess the severity of impairments associated with CFS at baseline and chart which, if any, of these measures showed change after treatment. Most importantly, any improvements in a patient's current state of health status would ideally be reflected in improvements in other areas of psychopathology (such as mood). We had already shown that improvements in current state of health status in the untreated patient led to a decrease in the number and severity of symptoms recorded and improved sleep.

Table I describes the various questionnaire measures used in the present study. The questionnaires administered were completed by the patient at home in their own time, thus minimising the possibility of questionnaire fatigue.

Mood and performance testing. Performance test data were collected using a Viglen Dossier laptop computer connected to a simple 3-button response box (Smith et al., 1996). During the testing session, which lasted approximately fifteen minutes, ratings of mood, memory, cognitive vigilance and simple reaction time were recorded. The tasks themselves were as follows:
Mood Scales: Subjective mood was assessed using 18 computerised visual analogue mood scales. Each of the 18 bipolar scales being composed of a pair of adjectives for instance, drowsy — alert or happy — sad. Participants were required to move the cursor (using the response keys marked with arrows left and right) from a central position on the scale anywhere along the horizontal rule, towards either extreme of the scale, until the cursor rested at a position which was representative of their mood state at that exact time. These 18 scales were presented successively. For each of the scales a score was recorded between 1 and 51. Using a factor analysis, three scores were derived from the 18 scales; alertness, hedonic tone and anxiety. Free Recall: This assessed episodic memory. The participants were shown a list of 20 words presented at a rate of one every two seconds. At the end of the list the volunteer was given two minutes to write down (in any order) as many of the words as possible on a sheet of paper provided. The variables measured were the number of words written down, the number of correct words and the number of incorrect words recorded. Variable Fore-Period Simple Reaction Time Task: In this task a frame of a box was displayed in the centre of the screen and (at varying intervals from 1–8 seconds) a target square appeared inside the box. As soon as the participant detected the square, they were required to press the response key marked SPACE using the forefinger of their dominant hand only. A reaction time was measured for each presentation. A mean reaction time was calculated for each minute of performance on the basis of the number of trials completed per minute. The total number of trials completed over the duration of the task was also recorded. An overall mean reaction time was calculated from the total number of trials completed over the duration of the task. Repeated Digits Detection Task: This visual cognitive vigilance task measured the ability to detect targets at irregular intervals. In this task participants were shown successive presentations of three digit numbers in the centre of the screen (e.g. 473) at the rate of 100 per minute. Each three-digit number usually differed from the one immediately preceding it, with one out of the three digits being replaced with a different digit (e.g. 463, 563, 562). Occasionally (8 times a minute) the same three-digit number was presented on successive trials. It was these repetitions that the participant needed to detect and respond to as quickly as possible by pressing the space key on the keyboard using the forefinger of their dominant hand. For each minute of the task and over the duration of the task the total mean reaction time to targets, the total percentage of trials correctly detected and the total number of false alarms were measured.

Results

Data were analysed using paired sample t-tests at baseline/post-therapy and baseline/six-month follow-up, analysis of covariance post-therapy and at six month follow-up, with baseline scores as the covariate, and chi-squared tests for the categoric questionnaire data.

Patient demographics and illness history

Data from previous studies had highlighted the differences between CFS patients and a matched control group using a variety of subjective and objective measures (Thomas and Smith, in preparation). Table II shows the patient demographic and illness history for those recruited to the study. These data show that the groups conform to the general profile of CFS sufferers, i.e. the sample being predominately married females in their forties and the baseline characteristics of this cohort corresponds to data from previous findings (Thomas and Smith, in preparation). There are no significant differences between the three groups at baseline.

Table II. Baseline demographic data for the three patient groups.

<table>
<thead>
<tr>
<th></th>
<th>MCT N=12</th>
<th>Relaxation N=14</th>
<th>Controls N=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>33.3%</td>
<td>28.6%</td>
<td>33.3%</td>
</tr>
<tr>
<td>Female</td>
<td>66.7%</td>
<td>71.4%</td>
<td>66.7%</td>
</tr>
<tr>
<td>Marital Status:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>58.3%</td>
<td>71.4%</td>
<td>55.6%</td>
</tr>
<tr>
<td>Mean Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>46.67</td>
<td>(8.05)</td>
<td>46.22</td>
</tr>
<tr>
<td></td>
<td>45.71</td>
<td>(12.56)</td>
<td>41.04</td>
</tr>
<tr>
<td>Length of illness (months)</td>
<td>78.75</td>
<td>(56.59)</td>
<td>114.00</td>
</tr>
<tr>
<td></td>
<td>104.14</td>
<td>(74.06)</td>
<td>(51.13)</td>
</tr>
<tr>
<td>Current State of Health:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worse than at any stage of the illness</td>
<td>16.7%</td>
<td>7.1%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Bad</td>
<td>25.0%</td>
<td>57.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Bad with some recovery</td>
<td>41.7%</td>
<td>14.3%</td>
<td>44.4%</td>
</tr>
<tr>
<td>Recovering with occasional relapses</td>
<td>16.7%</td>
<td>21.4%</td>
<td>44.4%</td>
</tr>
<tr>
<td>Almost completely recovered</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Total Symptom Score</td>
<td>18.58</td>
<td>(5.33)</td>
<td>13.89</td>
</tr>
<tr>
<td></td>
<td>17.64</td>
<td>(5.37)</td>
<td>(4.73)</td>
</tr>
</tbody>
</table>
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Figure 1. Alertness scores immediately post-therapy and at 6 month follow-up with baseline scores as covariate. Higher scores = greater alertness. (Scores are the group means with standard error values shown as bars).

Measures of mood and performance

Mood. Analysis of covariance demonstrated significant improvements in the MCT group in terms of alertness post-therapy (F(2,31) = 3.31, p < 0.05; MCT = 233.9, Relax = 176.1, control = 170.1, see Figure 1). Pairwise comparison at six-month follow-up revealed that MCT and control groups remained significantly different (mean difference = 58.08, se = 25.98, p < 0.033). There were no significant changes in hedonic tone or anxiety.

Within group comparisons of mood indicate a significant improvement in alertness in the MCT group at the post-therapy (t = 3.269, df = 11, p < 0.007) and six-month follow-up assessments (t = 3.039, df = 11, p < 0.011). Patients in this group also report reduced levels of anxiety post-therapy (t = 2.252, df = 11, p < 0.046) and at six-month follow-up (t = 2.514, df = 11, p < 0.029). They do not, however, show significant improvements in hedonic tone at either time point.

The Relaxation group produced significant improvements in alertness at six-month follow-up (t = -2.500, df = 13, p < 0.027) and a significant reduction in anxiety at six-month follow-up (t = -3.842, df = 13, p < 0.002). There were no other significant findings in the mood and performance data for the Relaxation group and there were no significant within group differences in any of the mood and performance data for the controls.

Performance. There was no main effect of treatment group on mean reaction time immediately post-therapy, however, pairwise comparisons showed a significant difference between the MCT and control groups (mean difference = -79.16 ms, se = 34.62, p < 0.029). At six month follow-up there was a main effect of treatment group on mean reaction time with a significant improvement in the MCT group (F(2,31) = 3.34, p < 0.048; MCT = 374.0 ms, Relax = 436.4 ms, control = 444.2 ms, see Figure 2).

The word recall and vigilance tasks did not yield any significant differences between treatment groups either immediately post-therapy or at six-month follow-up.

Within-group comparisons were made between baseline and immediately post-therapy sessions, and baseline and six month follow-up sessions for all mood and performance variables. Significantly more words were recalled correctly at six-month follow-up (t = 3.464, df = 11, p < 0.005) in the MCT group. Analyses of the vigilance tasks showed that there were also significant improvements in the MCT group for mean reaction time post-therapy (t = 2.845, df = 11, p < 0.016) and at six-month follow-up (t = 3.671, df = 11, p < 0.004). Data from the repeated digits vigilance task also indicated a significant improvement for the MCT group in the total number of repeats correctly identified both immediately post-therapy and at six-month follow-up sessions (t = 3.529, df = 10, p < 0.005; t = 2.254, df = 10, p < 0.048 respectively) indicating improved vigilance.

Questionnaire data

Sleep. Data described in Figure 3 indicate that MCT was associated with improved sleep quality. Improvement was assessed by creating a variable reflecting “better” or “much better” sleep (χ² = 14.222, df = 4, p < 0.007, MCT = 83.3% improved sleep, Relax = 28.6% improved sleep, control = 11.1% improved sleep). This improvement was maintained at six-month follow-up.

Figure 2. Mean Reaction Time scores at baseline (base), post-therapy (p/ther.) and six month follow-up (6 mths). Lower scores = faster reaction times. (Scores are the group means with standard error values shown as bars).
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Table III. Percentage change values at six month follow-up (positive values = positive outcome).

<table>
<thead>
<tr>
<th></th>
<th>MCT</th>
<th>Relaxation</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Mood</td>
<td>146.07 (123.91)</td>
<td>47.71 (17.92)</td>
<td>52.55 (25.15)</td>
</tr>
<tr>
<td>MOS sf 36:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Health</td>
<td>90.26 (21.62)</td>
<td>48.21 (22.70)</td>
<td>15.20 (9.73)</td>
</tr>
<tr>
<td>Fatigue Problem Rating</td>
<td>26.01 (5.96)</td>
<td>17.47 (9.25)</td>
<td>6.98 (8.91)</td>
</tr>
<tr>
<td>Cognitive Failures Questionnaire</td>
<td>16.06 (7.85)</td>
<td>3.93 (6.22)</td>
<td>5.04 (7.84)</td>
</tr>
</tbody>
</table>

Fatigue, physical and mental health and cognition. Percentage change scores were used in the following analyses. Table III demonstrates that MCT has a measurable benefit for CFS patients. Positive mood, general health (as measured by the MOS sf 36), fatigue problem rating scale and cognitive failures questionnaire reveal positive outcomes for the patients in the MCT group. However, there were no significant improvements following MCT for depression and anxiety scores.

General health and quality of life. The MCT group show very encouraging outcomes when considering ratings of general health and quality of life. When considering the current state of health measure taken from our previous studies, significantly more of the MCT group reported improvements than the Relaxation or control groups ($\chi^2=9.78$, df = 4, $p<0.044$, MCT = 83.3% improved health, Relax = 50.0% improved health, control = 22.2% improved health). This positive outcome was coupled with significantly lower mean total symptom scores (F(2,31) = 4.627, $p<0.017$, MCT = 9.31, Relax = 14.27, Control = 15.95). The MCT group also reported significant improvements in activity levels ($\chi^2=29.670$, df = 4, $p<0.000$, MCT = 100% improved activity, Relax = 21.4% improved activity, control = 42.9% improved activity) (Figures 4–6).

The beneficial nature of MCT is further highlighted in terms of lower physical symptoms scores, lower anxiety, depression and perceived stress scores and reduced mental and physical fatigue scores. MCT patients also recorded fewer cognitive difficulties, lower emotional distress and fewer somatic symptoms (both post-therapy and six months later) than the Relaxation and control groups. However, the data here did not reach statistical significance but the general trend appears to indicate that improvements in these areas are occurring.

Discussion

We have shown in our longitudinal study of the untreated CFS patient that one would expect to see a spontaneous recovery rate of only 6% over a six-month period. Recovery was calculated using a variable which can not only allow the patient to accurately assess their health status at any given time, but has also been shown to be associated with changes in the number of symptoms reported and subjective measures of positive affect (Thomas & Smith, in preparation). We also concluded that changes in this variable were associated with patients reporting improved sleep quality. Breaking the downward spiral of poor sleep quality and reduced activity levels reported by CFS patients, which exacerbates existing symptoms, is considered to be a major step on the road to recovery. Before this can begin,
What does this study tell us?

- Patients receiving MCT reported significant improvements in sleep and increased levels of activity.
- Patients also reported feeling significantly more alert after treatment and were less anxious.
- The most important finding is a significant improvement in the mean reaction time of the simple reaction time task.

however, the patient must first be persuaded that increasing activity levels will not have an adverse effect on their illness. Therefore, the initial stages in the MCT programme examine each patient's views and attempts to dispel preconceptions they may have regarding exercise. This is reflected in the fact that we see no significant improvements in our measures at the mid-therapy assessment point.

When applying the current state of health measure in this study, improvements of 83% in the MCT group compares favourably with outcome measures used in other CBT and GET trials which demonstrate improvements of 70% and 80% respectively. Significant reductions in total symptom scores in the MCT group has also re-enforced the view that this variable can accurately assess changes in patients' health status and, therefore, can be used as a predictor of outcome. Patients receiving MCT reported significant improvements in sleep and increased levels of activity. Past research has shown that impairments in both sleep and activity are confounding factors in perpetuating the illness. Patients also reported feeling significantly more alert after treatment and were less anxious.

Overall, patients in the MCT group reported improvements in many of the areas assessed, reaching statistical significance for the current state of health both immediately post-therapy and at six month follow-up. Within group comparisons provide data showing that patients in this group reported significant improvements in alertness and anxiety scores immediately post-therapy. Furthermore, these improvements were maintained at the six-month post-therapy assessment indicating sustainability. Measures of performance in the MCT group also provided significant improvements in terms of word recall, mean reaction time (in the simple reaction time task) and increased repeated digits detection in the vigilance task. Although the Relaxation and control groups did not record any significant improvements in terms of performance, the Relaxation group did produce a significant increase in alertness and lowering in anxiety levels six months post-therapy.

Benefits of Relaxation Therapy are indicated here, especially with regard to reducing psychopathology. This, therefore, confirms the beliefs of some patient groups that Relaxation sessions offer some symptom relief. Relaxation Therapy is normally incorporated into the MCT technique and was only omitted from the study to act as the comparison group. It is reasonable to predict, therefore, that inclusion of Relaxation Therapy in MCT can only enhance its effectiveness, especially in reducing psychopathology.

Our most important finding is a significant improvement in the mean reaction time of the simple reaction time task in the MCT group, a measure known to correlate with functional indicators such as walking tests. This is the first study to demonstrate improvements in objective measures of function in these patients. Previously, measures used to assess treatment efficacy have relied on patients subjectively rating their health in terms of fatigue and/or disability. In this study, the subjective improvements recorded by patients have been substantially enhanced by quantitative data from objective tasks.

In the light of findings from our previous studies that spontaneous recovery rates in CFS are very low, the results of this trial are encouraging. The objective improvements in cognitive performance demonstrated in this study are unique and important from a treatment point of view. While the MCT technique developed here is an exciting step forward in CFS therapy, there remains one issue to be addressed namely the role of the therapist. Manuals can, and have been written detailing aspects of CBT, GET and Relaxation Therapy techniques. The fundamental question that we need to address next is whether MCT is effective when provided by another therapist. Future research should be centred on a training programme for therapists and their assessment. We can then confidently offer a proven therapy to a wider number of CFS patients, ideally in the primary care setting. It is also recommend that further assistance is required to aid diagnosis at the primary care level to negate the need for numerous costly outpatient consultations. In addition, it would be of interest to survey the current group of patient volunteers to assess their health over a longer time period and to invite views on the service provided. Patient feedback could then be used to assist the development of a more formal protocol for MCT.

Acknowledgements

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References


Multi convergent therapy for the treatment of CFS


A multiconvergent approach to the rehabilitation of patients with chronic fatigue syndrome: a comparative study

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Abstract

Objectives This study investigated the efficacy of a rehabilitation technique for the treatment of chronic fatigue syndrome that was developed by a physiotherapist. Data collected retrospectively from a pilot study indicated that patients benefited from this multiconvergent approach, so further assessments were warranted.

Design Treatment efficacy was assessed by comparing the primary and secondary outcome measures of patients attending multiconvergent therapy (MCT) with those of patients attending relaxation therapy and a group of non-intervention controls.

Setting The active treatment took place at a clinic within the physiotherapy outpatient unit. Relaxation therapy and all assessments were conducted at the psychology unit.

Participants Thirty-five participants, fitting the Centers for Disease Control and Prevention criteria for chronic fatigue syndrome, were recruited from two outpatient clinics and an existing patient panel.

Intervention Patients were assigned to either MCT (n = 12) or relaxation therapy (n = 14). Nine participants who received general medical care were used as a comparison group.

Main outcome measures The Karnofsky performance scale was used as the primary outcome measure of function. Secondary outcome measures assessing overall improvement in patient condition, fatigue and disability levels were also administered.

Results A significant percentage of the patients attending the MCT sessions showed improvement in the primary outcome score used to measure the success of the treatment (MCT = 83%, relaxation = 21%, controls = 0; P < 0.001). A significant percentage of this group also reported improvement in their overall condition (MCT = 92%, relaxation = 64%, controls = 22%; P < 0.001), lower fatigue levels (MCT = 83%, relaxation = 57%, controls = 11%; P < 0.001) and lower levels of disability (MCT = 75%, relaxation = 43%, controls = 11%; P = 0.032) immediately after post-therapy. In addition, these improvements were maintained at 6-month follow-up.

Conclusions Outcomes from this small preliminary study were encouraging. The multiconvergent approach produced significant improvements for standardised primary and secondary outcome measures. Further research is required to examine the efficacy of this approach over time, and its effectiveness on a larger scale within the primary healthcare setting using additional therapists trained in the technique.

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Keywords: Chronic fatigue syndrome; Cognitive behaviour therapy; Graded exercise therapy; Rehabilitation

Background

Chronic fatigue syndrome (CFS) is an illness that produces a marked reduction in activity and an increase in mental fatigue. It is also accompanied by four or more co-existing symptoms including those of a cognitive or neuropsychiatric nature. The illness (by definition) must be of at least 6 months duration and of sufficient severity to cause substantial functional impairment [Centers for Disease Control and Prevention (CDC) criteria] [1]. The symptoms associated with the illness can be very debilitating and persistent with little spontaneous recovery [2,3].

Evidence from a review of epidemiological studies [4] suggests that, in large-scale surveys, up to half of the general population would report suffering fatigue-like symptoms during their lifetime. Twenty percent of these would subsequently seek medical care. However, in the majority of cases,
the fatigue experienced could be explained by other mitigating circumstances and, therefore, the incidence of CFS in the general population is relatively low. The low incidence should not, however, detract from the severe effect that the illness has on the individual sufferer. The decrease in personal, occupational and social activities that accompanies the illness instills a sense of frustration and hopelessness within the patient. In addition, financial concerns have been raised regarding the increased uptake of unemployment benefits and the drain on healthcare resources brought about by the illness [5,6].

As both the cause and the pathophysiology that maintains CFS are unknown, treatments have been investigated on a pragmatic basis. Previous research has suggested that once CFS is established, cognitive, behavioural, emotional, physiological and social factors work together to perpetuate the illness [7]. In addition, studies into the cognitive deficits associated with CFS have suggested that the impairment in functioning observed in CFS is similar to that seen in sleep disorders and physical deconditioning [8]. It is not surprising, therefore, that systematic reviews of possible management protocols for CFS cite approaches such as cognitive behaviour therapy and graded exercise therapy as the most consistently effective forms of intervention for this illness [9]. Indeed, studies investigating the efficacy of cognitive behaviour therapy have verified this in 68% of trial participants. Furthermore, this statistic compares favourably with the 36% of patients reporting benefit from relaxation therapy [10]. Similarly, exercise therapy has shown great promise for improving illness outcome in CFS patients [11]. Significant changes in functional status and general fitness are indicated when applying this approach to CFS. In addition, it has been demonstrated that simply educating patients about the benefits of exercise can also increase levels of activity in sufferers [12]. The use of cognitive behaviour therapy and graded exercise therapy (separately or in combination) as treatment strategies for CFS has, therefore, been the subject of several randomised controlled trials.

A clinic was set up at a physiotherapy outpatient department in 1991 to provide a service specifically for patients whose condition did not respond to first-line medical intervention and for patients where no solution was readily available. Multiconvergent therapy (MCT) was developed to tackle a wide range of medically unexplained symptoms including tinnitus, vertigo, anxiety, hyperventilation syndrome and irritable bowel syndrome.

The MCT regime described in the current study reflects Engel’s biopsychosocial and philosophical approach to health outcome [13]. The therapy also mirrors the work of physiotherapists in the field of chronic pain management who advocate a more active integrative role for therapists in the assessment and management of beliefs and emotions [14,15].

The success of MCT in the management of tinnitus and irritable bowel syndrome [16,17], which are often reported as co-existing symptoms within CFS, prompted the inception of a pilot study to ascertain its suitability in the treatment of CFS. Participants for the study were recruited from a CFS research outpatient clinic specifically set up to investigate all aspects of the illness.

Anecdotal reports from the pilot study indicated that sufferers were benefiting from the treatment. Therefore, a retrospective study was conducted on the 28 patients who had taken part in the scheme for quantification. Each patient received a questionnaire through the post. The objective of the study was to produce a quick and effective outcome measure to elicit their overall CFS status. Eighteen of the 28 patients (64%) responded to the follow-up call both post-therapy and 2–3 years later. Five of the 10 non-responders had moved away with no forwarding address, and the remainder did not reply. This resulted in an 82% response rate based on contactability. At the post-therapy time point, 16 of the 18 respondents regarded their CFS as ‘better’ (88%) and two respondents reported no change in their condition (22%). At 2–3-year follow-up, 13 of the 18 respondents continued feeling better (72%), one reported no change in their condition (5%), and four (22%) reported feeling ‘worse’ [18].

Although these exploratory findings were encouraging, additional, more rigorous studies were needed. The logical progression for the research, and the aim of the current study, was to test the efficacy of the combination therapy (MCT) by incorporating measures validated in previous studies into CFS treatment efficacy. The primary and secondary outcome measures chosen for the current study had been widely used and validated in previous treatment trials for CFS [10,19], which enabled comparison of MCT on a like-for-like basis. In addition, similar comparison groups were employed as used in previous treatment trials.

Methods

Design

Between-group comparisons were used to assess the efficacy of MCT compared with the relaxation and control groups both immediately post-therapy and at 6-month follow-up.

Participants

Appropriate ethical approval was granted by the local health authorities covering the outpatient clinics. All of the participants in the study were recruited through a single consultant physician who had diagnosed their condition. Referrals to the specialist clinic followed standard National Health Service protocol. On attending the clinic, each patient was informed of the nature of the study and invited to participate. Recruitment continued until the closure of the clinic in 2001. Subsequent volunteers were recruited from an infectious diseases outpatient clinic run by the same physician.

The participants were made aware at the initial consultation that they would not receive further appointments with the attending physician until the 6-month post-therapy assess-
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ment point. This was not to say that the patient was denied medical care, but if it was necessary for the patient to revisit the clinic before the 6-month follow-up appointment, they could no longer take part in the study. Informed consent was obtained from all patients participating in the study. It was made clear that it was possible to withdraw from the study at any stage without repercussions.

As relaxation therapy had already been used to alleviate the symptoms of CFS with some success (see below), it was decided that a separate control group would be necessary to act as further comparison. The control group comprised CFS patients who received standard medical care. Their data were used as an estimate of the untreated illness.

Inclusion criteria

The inclusion criteria for the study were that participants had to: (1) meet the CDC criteria for CFS [1]; (2) be willing to attend all therapy and assessment sessions; and (3) have a Karnofsky performance score of 70% or less [19]. A score of 70% or less implies functional impairment at a level that makes full-time employment impossible.

Exclusion criteria

Patients were excluded from the study if their fatigue was due to other mitigating circumstances.

Sample size

Sample size calculations based on previous work suggest a recovery rate of 72% among those receiving MCT [18] compared with 6% for untreated controls (data from ongoing longitudinal study). Therefore, a study of eight MCT recipients and eight controls would have an 80% chance of detecting a treatment effect at the 5% level of statistical significance.

Materials

Primary outcome measure

The main indicator for successful treatment outcome was the Karnofsky performance scale, as used by Sharpe et al. in their randomised controlled trial of cognitive behaviour therapy for the treatment of CFS [19]. Here the patient is categorised according to their functional performance on a scale of 0–100%. Karnofsky performance data were collected at the initial clinic visit (baseline) and at 6-month follow-up by the consulting physician. Success of the treatment was measured by the attainment of a score of 80% or more at 6-month follow-up and/or an improvement in performance scores of 10% or more at this time point.

The Karnofsky scale was also presented to patients at baseline, immediately post-therapy and at 6-month follow-up. The scale was modified, however, by removing the more catastrophic lower elements. This enabled the authors to assess the ability of patients to monitor improvements subjectively.

Secondary outcome measures (global measures of illness and satisfaction with treatment)

Patients rated any improvements in their condition immediately post-therapy. Ratings of overall improvement in their condition and changes in fatigue and disability were recorded on Likert-type scales [10]. Each scale ran from extreme negative through 'no change' to extreme positive responses. In addition, patients were asked to rate any further changes from the post-therapy measures at 6-month follow-up using the same scales.

Patients rated the usefulness and their satisfaction with the treatment on Likert-type scales, and were also asked if they would recommend the therapy to other CFS sufferers.

Procedure

Each patient attending the clinic was assessed by a consulting physician specialising in CFS. If the patient met the study criteria, they were invited to take part in the study and their baseline Karnofsky performance score was recorded. All further treatment protocols and patient assessments were conducted at either the physiotherapy outpatient department (MCT) or the psychology research unit (relaxation and control).

The two treatment groups received approximately 10 1-hour sessions on a one-to-one basis. Ten sessions were chosen for two reasons: this represented the length of the relaxation protocol; and the MCT technique typically ran for eight to 12 sessions (depending on the needs of the patient). The control group was assessed over a similar time period based on attendance at 10 weekly sessions.

The patients were re-interviewed by the consulting physician at 6-month follow-up with their functional performance score duly recorded. Patient-rated primary and secondary outcome measures were also collected immediately post-therapy and at 6-month follow-up. Data collection for the study took place over an 18-month period.

Treatment assignment

Due to the small numbers in the study, patients recruited into the trial were assigned to a treatment group individually. Referral letters for both the MCT clinic and the relaxation therapist were prepared for each patient who agreed to participate. These were placed in envelopes addressed to both therapists. Both envelopes were then placed into a larger blank envelope. One envelope was selected by a colleague who was blinded to the study’s protocol. The blank envelope selected was opened and the letter was sent to the appropriate therapist. The other letter was shredded. The patient was contacted by the chosen therapist and subsequent assessment appointments were made through a third party.

The control group was recruited separately from the active arms of the study. Due to the imminent closure of the CFS clinic, it was decided to complete as much of the active arms of the study as possible before recruitment of the non-intervention control group. The controls comprised members
of the CFS research panel who had been recruited for previous studies carried out at the centre.

**Masking**

Both the consultant physician recruiting the patients and the researcher conducting the assessments remained blind to the therapy group of each participant until after the 6-month follow-up assessment when the treatment codes were revealed.

**MCT rationale**

MCT employs cognitive behavioural therapy and graded exercise therapy in combination with appropriate interventions to improve sleep quality and to treat any comorbid mood disturbance.

The cognitive behaviour therapy aspect of MCT aims to identify factors that can be seen to predispose, precipitate or perpetuate the illness and improve sleep quality. This phase of MCT also involves cognitive restructuring of dysfunctional beliefs, thoughts and behavioural patterns whilst re-inforcing positive beliefs, thoughts and behavioural patterns.

The graded exercise phase of MCT involves the introduction of planned activity and rest (referred to as ‘pacing’). Non-prescriptive graded exercise is introduced after the patient has explored the relationship between fatigue and cognition. The rationale follows a model similar to that suggested by Noakes et al., who hypothesised that physical activity and the recruitment of skeletal muscle units is controlled by a continuous pacing strategy within the central nervous system based on its feedback from physiological and psychological systems [20]. Gentle walking is introduced every second day at a level appropriate for each person in order to prevent postexercise malaise. The distance and time walked is increased as the patient’s confidence grows. The patients themselves are responsible for increasing the level of exercise and providing feedback at the therapy sessions.

Mindfulness (or insight) meditation is also blended with the cognitive behaviour therapy/graded exercise therapy approach. Patients are encouraged to fix their thoughts in the present without being distracted by the associations attached to those thoughts or sensations (such as pain), and, as a result, are able to reduce the suffering associated with physical somatic disorders [21–23]. Patients can then use the technique during times associated with heightened awareness of pain or fatigue (such as during exercise). In addition, this method can be used to reduce any intrusive thought patterns experienced at night that prevent the patient from falling asleep [24]. This technique has proved useful in other conditions associated with pain, immune function, sports and cardiopulmonary function [25–28].

Heart rate monitors are used during the sessions to act as a symbol of fitness and wellness, to help vulnerable patients from deteriorating into a ‘boom and bust’ scenario, and to assess the relaxation response [24]. The monitors enable identification of the average peak heart rate for each patient whilst exercising at a sustainable level, and also establish cardiac rhythm. The monitors are not used to promote exercise within a given range for a number of reasons: (1) recent studies on exercise in fibromyalgia (a condition which overlaps substantially with CFS) show little correlation between cardiovascular improvement and improvement in CFS [29,30]; (2) the effect of stress on some patients with CFS may lead to chronic overbreathing (PaCO2 < 30 mg CO2) during exercise (unpublished data from the CFS clinic); and (3) although improvements in patients with CFS have been observed in previous graded exercise therapy trials, exercise should not be insisted upon in all cases [11].

**Relaxation therapy rationale**

The relaxation procedure used in this study is based on the work of Ost [31]. The use of the rapid relaxation technique has not been limited to CFS but has proved successful for a wide range of problems such as tinnitus and pain. The aim of this type of procedure is to help patients to target specific areas of the illness, thus facilitating symptom relief. Rapid relaxation, therefore, offers the patient a way of coping with and managing their symptoms. The therapist guides the patient through the relaxation technique over a period of 10 weeks, with each session revising the previous session before moving on to a different major muscle group. Relaxation therapy has been favoured by various centres and patient groups (e.g. Action for ME) throughout England, Scotland and Wales, and has been used as a comparison by other research groups [10].

**Data analysis**

Chi-squared tests ($\chi^2$) were used to compare the proportions in each group attaining normal function (80%) on the Karnofsky scale and/or an improvement of 10% or more from the baseline scores. The effect of MCT on the secondary outcome was also assessed using $\chi^2$ tests (post-therapy and 6-month follow-up).

**Results**

**Patient demographics and illness history**

Of the 87 possible participants attending the CFS clinics during the recruitment phase of the study, 40 patients took part in the study. The remainder either: (1) did not meet the study criteria; (2) did not have CFS; or (3) refused to participate. Seventeen participants were assigned to MCT, 14 to relaxation therapy and nine to the control group. Five subsequently withdrew from the study: one due to family problems, one strongly believed that they were not suffering from CFS, and three failed to attend their first therapy session. All five had been assigned to the MCT group. The patients who did not attend the first treatment session were contacted on three separate occasions but did not respond to the therapist’s correspondence.
3.10 Paper 10

Table 1
Baseline demographic and clinical characteristics by group

<table>
<thead>
<tr>
<th></th>
<th>Multiconvergent therapy (n = 17)</th>
<th>Relaxation (n = 14)</th>
<th>Control (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male</td>
<td>29%</td>
<td>29%</td>
<td>33%</td>
</tr>
<tr>
<td>Married</td>
<td>59</td>
<td>71</td>
<td>56</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>48 (8.03)</td>
<td>45 (12.56)</td>
<td>46 (11.04)</td>
</tr>
<tr>
<td>Diagnosed by a GP</td>
<td>56%</td>
<td>50%</td>
<td>67%</td>
</tr>
<tr>
<td>Length of illness (months), mean (SD)</td>
<td>80 (48.43)</td>
<td>105 (73.1)</td>
<td>114 (51.1)</td>
</tr>
<tr>
<td>Depression scores* (SD)</td>
<td>20.47 (10.4)</td>
<td>20.43 (7.3)</td>
<td>16.44 (13.5)</td>
</tr>
</tbody>
</table>

SD, standard deviation; GP, general practitioner.
* Beck Depression Inventory [32].

Table 2
Patient- and consultant-rated Karnofsky performance scores at initial clinic assessment (baseline)

<table>
<thead>
<tr>
<th>Karnofsky scores—number per cell</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-rated</td>
<td>1</td>
<td>3</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>Consultant-rated</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>27</td>
</tr>
</tbody>
</table>

Table 1 shows patient demographics, illness history and psychopathology scores for the three groups at baseline.

These data provide the typical demographic characteristics usually associated with CFS, namely that the sample was comprised predominately of married females in the fourth decade of life. There were no significant differences between the groups, although length of illness and depression scores [32] approached significance (P = 0.08 and 0.10, respectively). There were no significant demographic or clinical differences between the five participants who withdrew from the study and those who completed the study.

The Karnofsky performance scale (primary outcome measure)

Table 2 shows the data recorded by the patients and the physician at initial clinic interview (baseline).

The consultant rated all of the study participants between 60% and 70% on the functional performance scale. Although the patients were more likely to rate themselves on the lower elements of the performance scale, these data were not significantly different.

At the post-therapy time point, significantly more patients from the MCT group had attained normal functioning (i.e., a Karnofsky score of 80% or more) for the consultant-rated performance scores. This was also true for those attaining improvements of 10% or more.

This was mirrored in the patient-rated performance scores for both 80% functioning and 10% functional improvement (see Table 3).

There was no significant difference between the groups in terms of patient-rated performance scores immediately post-therapy for attainment of 80% or improvement of 10% or more.

Although these findings should be interpreted cautiously and could not be pursued further because of the small numbers involved, it appears that the association is robust.

Secondary outcome measures

Global assessment of function and satisfaction with treatment was made immediately post-therapy and at 6-month follow-up by the patient groups. At the post-therapy time point, the MCT group reported significantly greater improvement in their overall condition than the relaxation or control groups [χ² = 13.637, degrees of freedom (df) = 4, P = 0.009, MCT = 92%, relaxation = 64%, control = 22%]. This finding was repeated for the other two global outcome measures: (1) fatigue (χ² = 20.652, df = 4, P < 0.001, MCT = 83%, relaxation = 57%, control = 11%); and (2) percentage reduction in disability (χ² = 9.699, df = 4, P = 0.046, MCT = 75%, relaxation = 49%, control = 11%) (see Figs. 1–3).

At 6-month follow-up, the global outcome measures clearly show the longer-term benefits of MCT. The patients reported continuing benefits in terms of overall improvement in their condition (χ² = 24.481, df = 4, P < 0.001,

Table 3
Attainment of satisfactory outcome for performance scores (Karnofsky score of 80% or more) and improvement in performance of 10% or more at 6-month follow-up (patient- and consultant-rated)

<table>
<thead>
<tr>
<th></th>
<th>Multiconvergent therapy, % (n)</th>
<th>Relaxation, % (n)</th>
<th>Control, % (n)</th>
<th>χ², df, P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-rated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80% attainment</td>
<td>67 (8)</td>
<td>21 (3)</td>
<td>11 (1)</td>
<td>8.757, 2, P = 0.013</td>
</tr>
<tr>
<td>10% improvement</td>
<td>83 (10)</td>
<td>50 (7)</td>
<td>11 (1)</td>
<td>10.758, 2, P = 0.005</td>
</tr>
<tr>
<td>Consultant-rated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80% attainment</td>
<td>83 (10)</td>
<td>21 (3)</td>
<td>0 (0)</td>
<td>17.77, 2, P &lt; 0.001</td>
</tr>
<tr>
<td>10% improvement</td>
<td>83 (10)</td>
<td>36 (5)</td>
<td>44 (4)</td>
<td>6.377, 2, P = 0.041</td>
</tr>
</tbody>
</table>

df, degrees of freedom.
MCT = 100%, relaxation = 43%, control = 0%), lower levels of fatigue ($\chi^2 = 22.910, \text{df} = 4, P < 0.001, \text{MCT} = 67\%$, relaxation = 43%, control = 11%), and feeling far less impaired by their illness ($\chi^2 = 10.571, \text{df} = 4, P = 0.032, \text{MCT} = 83\%$, relaxation = 50%, control = 22%) than both the relaxation and control groups.

The lack of significant effects in the 'usefulness' and 'satisfaction' categories reflects the positive experience of patients during both MCT and relaxation therapy.

**Discussion**

The purpose of this study was to assess the efficacy of MCT in outpatients presenting with CFS who were under the supervision of a physiotherapist. CFS, although relatively uncommon, is a persistent, debilitating illness that has a profound effect on sufferers and their families. It was the increasing problem that this type of functional somatic syndrome was presenting to the medical profession which prompted the development of the management protocol discussed in the current study. MCT was developed by a chartered physiotherapist to address illnesses where the cause was unknown and treatment was unsuccessful. The therapy combines cognitive behaviour therapy and graded exercise in a holistic approach to illness management.

Findings from previous studies indicate that these two therapies were the most consistently successful forms of treatment for CFS. The rationale behind their success was that research had suggested that CFS patients appeared to be suffering from the effects of physical deconditioning [8], and cognitive, behavioural and sleep problems together with psychosocial factors seemed to be the mechanism responsible for perpetuating the illness [7,8].

Indeed, both cognitive behaviour therapy and graded exercise therapy had previously been evaluated separately and in combination. Therefore, an important consideration for the...
current study was the compatibility of the findings with those from previous studies. To this end, the outcome measures from two previously documented randomised controlled trials of cognitive behaviour therapy were included [10,19]. Similarly, CFS patients attending relaxation therapy were used as a comparison group. However, as relaxation therapy had already been used successfully in the management of CFS by patient groups, a group of non-intervention controls was recruited for further comparison.

Patients were recruited to the study by a CFS specialist who had diagnosed their condition. All patients met the CDC criteria for CFS [1] and their performance status was below 70% on the Karnofsky scale, indicating significant functional impairment. The Karnofsky score was subsequently used as a primary outcome measure. The success of the therapy was measured by the attainment of a performance score of 80% or more and/or an improvement in functioning above 10% at 6-month follow-up [19]. These data were recorded by the physician who remained blind to treatment assignment.

Data collected at the initial clinic assessment indicated no significant difference in the level of physician- and patient-rated functional performance. The patients, however, were more likely to select the lower elements of the scale to describe their impairment (i.e. greater functional impairment). Previous research, however, has indicated that patients with CFS do perceive their functional impairment to a greater extent than might actually be the case [33]. In the current study, there was no statistically significant difference between the physician and patient ratings of function; therefore, these data should not prove problematic. It would, however, be interesting to observe any changes in the ratings of impairment over time within the patient group.

Data collected by the patients indicated that there was no significant difference between the functional performance ratings for the three groups when comparing ratings immediately post-therapy with baseline measures. However, the secondary outcome measures employed [10] did indicate a significant improvement in overall condition, lower levels of fatigue and lower levels of disability in the MCT patients compared with the relaxation and control groups. These data indicate that although there was an improvement within the MCT group, patients had not interpreted it as a significant improvement in functioning.

By 6-month follow-up, however, the patients receiving MCT reported significantly higher scores on the performance scale than the relaxation and control groups. In addition, the MCT patients continued to report improvement in their overall condition, levels of fatigue and disability. Significant improvement beyond cessation of therapy is indicated here. When assessing acceptability, participants in the two treatment groups (namely MCT and relaxation therapy) commented that they were satisfied with the treatment offered and found it useful. These data further underline the positive effects of relaxation therapy reported by CFS patient groups.

The primary measure used to assess successful treatment outcome for the study was the consultant-rated Karnofsky scores at 6-month follow-up. The MCT group were significantly more likely to attain scores of 80% or above and were significantly more likely to show improvements in functioning of 10% or more at 6-month follow-up. Furthermore, statistical significance in the primary outcome measure seemed to be independent of demographic and baseline clinical characteristics.

Although this study provides data from a small number of CFS patients, the findings are encouraging. Time constraints, along with the imminent closure of the CFS clinic, meant that it was not possible to randomise the control sample or recruit substantially more patients, and these points are acknowledged as limitations in the study. However, the study was performed on a sample size likely to be found in a single, large general practice. Also, power calculations based on a previous study of MCT [18] suggested that even small sample sizes would demonstrate its benefits as a treatment for CFS. Therefore, the authors are cautiously confident that the MCT technique described in this paper produces measurable benefits in terms of improved functioning, and that these findings are directly comparable with other treatment studies [10,19].

Unlike previous studies, however, the authors believe that physiotherapists are best placed to implement this therapy, not only because the approach was developed by a practising therapist, but also due to the nature of the treatment. When implementing exercise regimes for CFS, it is important that the patient is guided through the treatment process carefully. Patients themselves are all too aware of periods of remission during which symptoms are less debilitating. This can lead to overexertion and can subsequently develop into several subsequent bad days for the sufferer. Forms of rehabilitation therapy must, therefore, consider the functional ability of each patient individually and address any psychosocial issues (such as emotional support and wellbeing) as they arise. In addition, therapists applying cognitive behaviour therapy and graded exercise therapy techniques for conditions such as CFS are required to adapt the approach constantly to suit the changeable nature of the illness.

With respect to the level of comorbid depression in the patient sample, recent findings have suggested that the abnormal psychopathology observed in CFS patients may not be responsible for their impaired functioning (submitted manuscript). However, it has also been shown that antidepressant therapy can assist long-term recovery in an otherwise untreated CFS patient [34], and these findings warrant further study. The use of antidepressant medication may play a role in the rehabilitation of the illness and has been employed previously. For the purpose of the current study, which was to assess the efficacy of MCT, antidepressant medication was not prescribed.

In continuing this programme of research, the authors are conducting a 3-year follow-up assessment of the study participants to evaluate the long-term effects of MCT (manuscript in preparation). Responses have been obtained from 24 of the study participants: two were no longer at the same address,
two declined to take part further and the remainder did not respond.

Twelve of the 14 patient responders who either attended relaxation therapy or were part of the control group have now been offered MCT. The patients will be re-assessed immediately post-therapy and at 6-month follow-up.

Acknowledgements

The authors would like to thank Dr MB Llewelyn for allowing access to his patients.

Ethical approval: None required.

Funding: Gatsby Foundation.

Conflicts of interest: None.

References


4 Methodological Considerations

Although the rationale and design used throughout the project was piloted on the first sixty-seven attendees at the Cardiff CFS research outpatient clinic, the scene was set by many years of research into the syndrome. Pivotal to this was the work conducted by Smith and colleagues (Smith, 1991; Smith, Behan, et al., 1993). Their findings not only provided the ground work for the methods used in later studies but provided the platform for successful grant capture. This seminal research explored methods by which the disturbances of memory, concentration and motor function reported by CFS patients could be objectively measured using computerised test batteries. Results from their study: “agreed with recent findings from other laboratories... it is now time to consider the nature of the neurological dysfunction underlying these effects” (Smith et al., 1993, p. 411).

4.1 The Study Participants

The 1991 Guidelines made recommendations about patient selection criteria and recruitment. The patients recruited from the CFS out-patient clinic conformed to the Oxford Criteria (Holmes et al., 1888) and later the Centre for Disease Control Criteria for Chronic Fatigue Syndrome (Fukuda et al., 1994) and were recruited to the study via consecutive NHS referral. Steps were taken to ensure that each patient volunteer was made fully aware of the nature of the research and that the project would involve participation over an extended period of time. As correct ethical procedure dictates, participants were informed that they could withdraw from the research programme at any time without adversely affecting any future healthcare provision and all patient data were coded in such a way as to protect anonymity. Ethical approval for the project was granted by the appropriate local health authorities at each stage of the research. The CFS
sufferers who completed the Action for ME service evaluation study were recruited directly by the charity and their data were treated with the same consideration as the Cardiff participant data.

4.2 Performance Measures

Due to the ever-changing nature of any on-going body of research, the methods used on the project were adapted to draw upon and develop previous methodologies. The cognitive performance task battery, for example, was reduced in size and task length following initial data analysis of the first cohort of sixty-seven patients. Although the longer test battery enabled the effects of acute fatigue to be investigated (Paper 1), it was considered that, as time was limited in the clinic environment, reducing the number and length of tasks in the test battery would maximise the number of participants tested whilst retaining the elements of the objective measures which provided vital data on the cognitive impairments associated with the illness. Of equal importance was the comfort of the patient. It was judged that unnecessarily lengthy testing sessions would only further distress already fatigued individuals. This might also alienate patients from participating in any future research conducted by the team.

There has been some debate surrounding the use of objective measures to assess performance and, in fact, the existence of any deficits in cognitive performance has been questioned (see Chapter 4 for further details). On reviewing the literature, Wearden and Appleby (1996) suggested that although measurable impairments were evident in the illness, they advised caution by suggesting that researchers consider the deficits patients report during their day-to-day experience of the illness and make attempts to reproduce these effects under experimental conditions (Wearden & Appleby, 1996).
The battery of tasks reported in the submitted manuscripts had already been used extensively to assess changes in cognitive performance under a variety of conditions. These included studies investigating the effects of the common cold, noise, caffeine and alcohol on mood and performance (Smith, et al., 1998; Smith, Thomas, et al., 1997; Smith, et al., 2000a, 2000b; Smith, Whitney, Thomas, Brockman et al., 1995; Smith, Whitney, Thomas, Perry et al., 1995; Smith, Whitney et al., 1997) as well as the fatigued state (in this instance, mental fatigue) (Smith, Brockman, et al., 1993). Furthermore, in light of preliminary data indicating that CFS sufferers appear to behave in a similar way to sleep-deprived healthy individuals (Paper 2), it is judged that these tasks are appropriate to detect any discrepancy in the patient group.

4.3 Questionnaire Measures

Conversely, the questionnaire aspect of the project increased over time in light of new findings emerging in the growing literature surrounding the illness. To make this more palatable, the patient volunteers were sent the questionnaires well in advance of their clinic appointment with the request that they complete them in their own time and at their own pace.

Keeping abreast of current trends was of particular importance when choosing additional tools for evaluating treatment efficacy (Paper 10). The need for comparability between studies had been highlighted in the Oxford consensus document (Sharpe et al., 1991). To address this, outcome measures from previous treatment trials were used in this study (Deale, et al., 1997; Sharpe, et al., 1996).

Methodological problems also arise when attempting to quantify recovery in CFS where bouts of remission are common. Outcomes from studies undertaken to estimate spontaneous recovery have varied widely between 8% and 63% (Cairns & Hotopf, 2005).
Having considered the literature, the large spread of scores reported can be attributed solely to the methods and/or criteria used to describe recovery. If a single measure of recovery were to be used, it would first have to be validated against other health-related outcome measures.

4.4 Statistical Considerations

The final, and by far the most important methodological factor to consider when attempting to quantify impairments in illnesses such as CFS is the heterogeneity of the patient sample as discussed by Wessely and his colleagues (Wessely, et al., 1996). The wide variety of symptoms present, together with the variability in their severity and frequency, have provided problems for researchers in the field and this is touched upon when describing the Cardiff patient sample (Paper 4). To limit the effect of heterogeneity it was important to collect data from a much larger patient sample and this provided the impetus to continue patient recruitment.

There were further methodological factors to consider when selecting the control comparison group. As the CFS patients here described are predominantly married females in their forties, any comparison group would have to reflect this particular demographic. Having matched the controls to the CFS patients in terms of age, gender, marital status and educational status, it was found that the pre-morbid intelligence scores of controls differed significantly from those of the patients – the patients more errors on the task than the controls. Pre-morbid intelligence was, therefore, identified as a confounding factor that may exert an independent effect on the chosen measures (such as an effect on motor speed, for example). The link between pre-morbid intelligence and cognition has already been identified in healthy controls (Jensen, 1987). To complicate matters further links between intelligence and co-morbid depression and between depression and cognitive performance have also been discussed previously (Brown, et al.,
This has major implications when attempting to compare CFS patients who not only seem to score less well on measures of premorbid intelligence, such as the National Adult Reading Test (NART; Nelson, 1982), than healthy controls but report also higher depression scores. Subsequent analyses were designed to take these two factors into consideration along with co-morbid anxiety (also known to affect cognition – Eysenck & Calvo, 1992) by using analysis of covariance (ANCOVA). Results from further ANCOVA subsequently highlighted fatigue scores and the total number of symptoms recorded by patients as independent factors exerting an independent effect on cognitive performance.

The research conducted was influenced by the aims, objectives and methodological considerations described above. The following section will discuss the outcomes of this programme of research in light of this and consider the contributions made to the scientific knowledge base.
5 Contribution to Knowledge

In order to contribute to the knowledge base, it was important to consider and address the recommendations made in the reports judged most influential in driving CFS research forward in the UK. The 1991 Guidelines for Research (Sharpe et al., 1991) made several important recommendations in order to reliably conduct and report studies on patients with CFS. In the first instance, the report provided preliminary definitions for five major symptoms of the illness which, the guidelines believed, warranted particular research attention. Three of these symptoms, namely fatigue, sleep disturbance and mood disorders, were investigated in the Cardiff CFS Research Project. Mood disorders will be discussed in this narrative in relation to the independent effect anxiety and depression exert on cognitive performance although they were not investigated explicitly. The role of mood disorders in CFS and their severity were examined in more depth by Farmer and colleagues (Farmer et al., 1995) and are not documented here.

Excessive fatigue is the primary presenting symptom in CFS. To investigate the nature of the fatigue experienced by sufferers it was important to examine its severity and to question whether CFS patients could become ‘more fatigued’ (Smith, Borysiewicz, et al., 1999). Subjecting an already fatigued individual to a task that is long in duration and/or monotonous made it possible to discover if participants would be able to compensate for the lowered alertness induced by the task as successfully as a non-fatigued individual. This study into the effect of acute fatigue on already fatigued (CFS) as opposed to non-fatigued control participants found that cognitive deficits worsened as a function of time.

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2 Studies conducted as part of the Cardiff CFS Project by the Department of Psychological Medicine, UHW
3 Paper 1
spent on the task. This time-on-task effect suggests an increased susceptibility to physical and mental fatigue over time (Smith, Borysiewicz, et al., 1999). By conducting further investigations with greater patient numbers it was possible to identify that this time-on-task effect was more apparent for one aspect of cognitive performance, namely motor speed (Thomas & Smith, in press). Comparisons between patient and control data for another three-minute test - the vigilance task – did not show the same phenomenon. One explanation for these seemingly contradictory findings is that the two tasks may require different processing mechanisms. This would form the basis for further studies as outlined in the next section of the narrative.

The next symptom recommended for further study - sleep abnormalities (Sharpe et al., 1991) - are of particular interest in CFS as patients frequently report difficulty falling asleep, spend less time asleep and complain that sleep does not refresh them, thus indicating poor sleep quality (Moldofsky, 1993; Moldofsky et al., 1988; Whelton et al., 1992). Preliminary findings provided evidence to suggest that deficits in vigilance, memory and attention were increased with abnormal sleep patterns (Smith, Thomas, et al., 1999) and it was considered important to investigate the extent to which these impairments reflect those seen in sleep deprivation. When a healthy individual is deprived of sleep there is an observed drop in cognitive performance (Smith, Brockman et al., 1993). It could be argued that the cognitive impairments observed in CFS were a direct result of sleep abnormalities. The investigation uncovered a sub-group of patients with sleep problems and showed that these patients also exhibited specific personality characteristics and physical and mental health problems (Smith, Thomas, et al., 1999). Deficits in memory, sustained attention and distractibility were also associated with

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4 Paper 4
5 Paper 3
patients reporting sleep problems, but motor speed was not. Sleep quality was, therefore, identified as a confounding factor when describing further cognitive deficits in the patient group (Thomas & Smith, in press). A final point of note when examining sleep in this illness was that, contrary to what one might expect, CFS sufferers do not report spending more hours asleep than healthy controls (Thomas & Smith, in press). There is, however, higher variance in the number of hours slept within the CFS group.

As outlined previously, initially research into CFS had centred on the investigation of possible causative agents including EBV and the enteroviruses. Although there was no evidence to suggest the role of infective agents in the aetiology of the condition, they had been implicated as possible means of exacerbating the illness (Smith, 1991). Anecdotally, patients themselves report symptoms of recurrent Upper Respiratory Tract Infections (URTI) but support for such anecdotal evidence had not been investigated systematically. The diary study conducted by Smith and colleagues (1999) was the first of its type attempting to address this (Smith, Thomas, et al., 1999). By keeping a weekly diary recording the incidence of URTIs over a three month period, the study confirmed patients’ claims that they were more susceptible to these infections. Data from this study were compared to comparable data collected over the same period from partners or friends of the sufferer. In this way, it was possible to ensure that both patients and controls were being exposed to similar infective agents. Together with an increased reporting of this type of infection in the patient group, the diary study also found that the level of URTI symptom severity was higher than shown in the control group. There are two possible explanations for the over-reporting of URTI symptoms in the patient group: it may be the case that sufferers are more sensitive to changes in physical sensations and translate these sensations into symptoms, thus resulting in the patient labelling symptoms as an illness (somatisation); alternatively it may simply be that
patients with CFS do suffer with more colds than the controls due to abnormal immune or endocrine function.

Despite the increased reporting of URTIs and the symptoms associated with them in the patient group, this type of infection does not appear to alter the severity of CFS itself as shown by subjective ratings. By incorporating the performance tasks into the experimental design it was possible to show that such infections failed to further compromise patients' cognitive functioning.

In line with the recommendation to identify factors associated with and responsible for perpetuating the illness (Sharpe et al., 1991), the study continued to examine the role of psychological factors in CFS. Psychosocial factors have, for example, been shown to have a major impact on physical and mental health. However, there had been no reports on the influence these factors may have on the severity of CFS. Preliminary data had indicated that psychosocial factors, support mechanisms and health-related behaviours may be implicated here (Smith, Borysiewicz, et al., 1999; Smith, et al., 1996). To examine their role further, both subjective questionnaire measures and objective cognitive performance tasks were used in a cross-sectional study design. The comparison group chosen to identify abnormalities within the patient group were age-, gender- and educational status-matched healthy controls. Continued recruitment from the outpatient clinic allowed a comprehensive description of a CFS patient sample on a scale previously not encountered in the literature together with more rigorous analysis of the cognitive

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6 Viral infection and chronic fatigue syndrome: a different approach (a final report to the Linbury Trust, Smith & Fox, 2000)

7 Paper 2
performance data collected - the results from which provide the topics for the following discourse.

The cognitive deficits associated with the illness have been the topic of some debate within the field of CFS research for a number of years. Indeed, their investigation was recommended in both the 1991 Guidelines and the 1996 Royal Colleges Report (Sharpe et al., 1991; Wessely, 1996). Where cognitive deficits have been reported, the nature of the impairment has varied (Capuron et al., 2006; Claypole et al., 2007; Davey et al., 2001; LaManca et al., 1998; Lawrie et al., 2000; Marcel et al., 1996). It is judged that data reported by Thomas & Smith (in press) make a significant contribution to this debate on a number of levels. In the first instance, the assertion that the deficits associated with CFS are solely a result of illness heterogeneity was addressed by collecting data from a large patient sample. Next, confounding factors known to exert an independent effect on cognitive performance, such as age, gender, co-morbid depression, pre-morbid intelligence, sleep quality and fatigue, were controlled for in the subsequent analysis. In addition, a review of the literature, together with further analysis, identified a correlation between cognitive failures and performance deficits and identified illness severity as the possible cause of the deficits reported. Finally, concern had been raised about the appropriateness of the tests used to measure the supposed cognitive impairments in previous studies (Wearden & Appleby, 1996). This was addressed by using a battery of tasks that had not only been rigorously validated previously in studies investigating the cognitive deficits associated with sleep deprivation and colds (Smith, Brockman et al., 1993; Smith et al., 1998), but were specifically chosen as they matched closely the cognitive problems reported by the patients themselves. When considering all the factors highlighted above, patients with CFS were shown to exhibit impairments in two aspects of performance – cognitive and motor functioning.
Together with cross-sectional studies, the 1991 Guidelines recommended that longitudinal studies be conducted to identify those factors associated with changes in CFS over time (that is, those which prolong the illness and those factors which impact on recovery). Many centres had attempted to identify factors which might predict recovery in the untreated illness. However, measuring recovery in CFS presents the researcher with a particular problem – the sufferer is highly likely to experience periods of symptom remission throughout the illness. In order to contribute to the scientific literature on recovery in CFS it was necessary, in the first instance, to identify and validate a measure which could accurately assess recovery (Thomas & Smith, submitted manuscript). A five-item scale, the current state of health measure developed in the preliminary stages of the research (Smith et al., 1996), was validated by comparing changes in health status recorded by the patient to their scores on other standardised health-related measures such as, for example, positive and negative mood, somatic symptoms and fatigue (Ray et al., 1993; Zevon & Tellegen, 1982). Once parity had been demonstrated, the patient sample completed this scale, together with a range of other subjective measures, at three follow-up time points – both six and eighteen months after their initial clinic visit and three years later. From these data it was estimated that recovery rates in the untreated CFS patient are low. It is this low spontaneous recovery rate that drives the need to increase research into viable treatment regimens. The longer the illness continues, the more entrenched negative illness cognitions become, contributing eventually to chronic disability. As a result, many sufferers become unable to work, often for long periods of time. To further complicate matters, it was revealed that unemployment at baseline was negatively associated with recovery over time, thus
further indicating the need for timely therapeutic intervention (Thomas & Smith, submitted manuscript).

Both the 1996 and the 2002 CMO reports stressed the need for research into possible therapeutic options for CFS. Preliminary descriptive analysis uncovered a sub-group of patients who had been prescribed antidepressant medication by their GP prior to their recruitment to the study. Longitudinal data analysis revealed that those patients taking antidepressant medication were significantly more likely to recover over time than those who were not (Thomas & Smith, 2006). Closer examination of these data identified that two antidepressant types — the Selective Serotonin Re-uptake Inhibitors (SSRI) and Tricyclics — were the predominant drugs prescribed to these patients. Antidepressant medication is often prescribed by General Practitioners (GPs) (as indicated in the survey study; Thomas & Smith, 2005), to address problems with sleep quality or mood disorders where present. However, randomised controlled trials (RCT) of the efficacy of antidepressants in the treatment of CFS had been inconclusive (Hickie et al., 1999; Natelson et al., 1996; Rimes & Chalder, 2005; Vercoulen et al., 1996; Wearden et al., 1998). Furthermore, anecdotal reports from those attending the Cardiff clinic indicated that, together with alcohol and caffeine, antidepressants are not well tolerated in the patient group and, where prescribed, attrition rates were high. In light of this, the Cardiff study produced some unexpected results. Between-group analysis indicated that recovery rates in those taking antidepressants were significantly higher despite the fact that there was no significant difference between the two groups at the initial clinic visit (baseline). In addition, and contrary to previous RCT data, patients in the antidepressant group reported lower levels of fatigue, better sleep quality and higher levels of activity at follow-

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up (Thomas & Smith, 2006): three factors that would be associated with improvement in the condition (Thomas, et al., 2006; Thomas, et al., submitted manuscript; Thomas & Smith, 2007). Further examination of these data suggests that the SSRI antidepressants were more likely to positively affecting recovery in the patient group than the Tricyclics.

It would appear then that the GPs completing the Cardiff survey were right to prescribe this type of medication to patients with CFS. The survey was conducted to assess the level of healthcare provision available to sufferers in Wales and to gauge whether GP views about CFS had changed in light of recommendations made in the 1996 and 2002 CMO reports (CFS/ME Working Group, 2002; Wessely, 1996). There was some concern regarding the breakdown in the relationship between doctor and patient, as well as the lack of trust and loss of confidence that inevitably results from this (Deale & Wessely, 2001). This was also raised as a major concern in the 2002 CMO report. Dissatisfaction at the apparent lack of interest GPs show has caused many patients to seek assistance from less reputable sources, namely the internet and its ever expanding provision of self-help information sites (Kisely, 2002). This is a medium rife with misleading advice which can be at best costly financially, but at the other extreme dangerous in terms of a patient’s health if one is not knowledgeable about which sites to use.

Unfortunately, the survey uncovered some disappointing findings, with half of those surveyed failing to recognise the existence of the disease (Thomas & Smith, 2005). Comparisons of patients’ primary care experiences when first developing the illness (up to ten years previously) and the way in which GPs currently manage people with CFS in

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12 Paper 8
their care are regrettably similar. Furthermore, the positive outcomes reported from several treatment trials conducted in England (Deale et al., 1997; Fulcher & White, 1997; Sharpe et al., 1996) had not filtered through to primary care in Wales and GPs were unaware of the treatment options available to their patients.

Finally, in order to increase the level of knowledge available to GPs in Wales to a level comparable to that of their colleagues in England as well as to fulfil the recommendations made by the CMO, two treatment efficacy studies were conducted. Westcare, a charitable organisation based in Bristol (which later merged with Action for ME), has for some time provided several management options for CFS sufferers nationwide, including residential rehabilitation courses and counselling services. A retrospective study of the suitability of the rehabilitation courses as a viable treatment option had produced promising results (Harrison et al., 2002) but these findings had not been subjected to rigorous scrutiny. Research into counselling as a treatment for CFS had been recommended in the 2002 CMO report (CFS/ME Working Group, 2002) and an efficacy study was indicated here. The development of reliable and reproducible measures to assess the illness in the cross-sectional and longitudinal studies outlined above (Smith et al., 1996; Smith, Borysiewicz, et al. 1999; Thomas & Smith, in press; Thomas & Smith, submitted manuscript) allowed the investigation of the effectiveness of these treatments in more detail. Furthermore, the inclusion of measuring tools used in previous efficacy studies (Deale et al., 1996; Sharpe et al., 1997) in the Cardiff project enabled comparisons to be drawn between research centres.

Evidence to support the efficacy of counselling in the management of patients with CFS, including improvements in both physical and mental fatigue scores (Chalder et al., 1993; Ray et al., 1993), has added to the evidence base. Patients receiving counselling also reported higher positive and lower negative mood scores and were discernibly less
anxious and depressed at follow-up. They also reported lower emotional distress, fewer somatic symptoms and lower perceived stress. Similar improvements in patient’s condition also provided evidence indicating the efficacy of the residential courses (Thomas & Smith, 2007).

The second treatment trial was conducted on a therapy that had been devised in Wales. Multi Convergent Therapy (MCT) had been developed to provide an NHS service to patients in Wales whose illness did not respond to conventional treatment regimes. However, as was the case with counselling and the residential courses, MCT had only been evaluated retrospectively.

Once again, in keeping with the Guidelines for Research (Sharpe et al., 1991) to the extend that the trial contributed to the evidence-base, steps were taken in devising the methodology to ensure comparability between the treatment efficacy studies conducted at Cardiff and those conducted previously in England (for example Deale et al., 1997; Sharpe et al., 1996). Treatment efficacy was evaluated in the form of a small RCT comparing MCT with patients attending Relaxation Therapy and those receiving standard medical care. Significant functional impairment was judged an important inclusion criterion for the study as it had already been established that poor health status was associated with poor prognosis in the untreated illness (Thomas & Smith, submitted manuscript). The outcome of the study was positive with improvements reported in the MCT group for many of the factors associated with CFS (Thomas et al., 2006; Thomas et al., 200815). Of particular note were improvements in levels of fatigue, improvements in sleep quality, increased levels of activity as well as improvements in overall health status (current state of health). The trial contributes to the evidence base by providing data

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supporting this therapy as a treatment vehicle for CFS patients in Wales. This includes data indicating a measurable improvement in memory and motor speed. This is the first time that objective measures have been used to assess treatment for this patient group (Thomas et al., 2006) and the improvement in memory and motor speed reported in the study provides further evidence for existence of cognitive deficit in this patient group.

There has, however, been some debate as to the long-term efficacy of behavioural therapies. Quarmby and colleagues (2007), for example, expressed caution that practitioners: ‘pay particular attention to relapse prevention and ensuring adequate follow-up in addition to continuing with cognitive-behavioural strategies once treatment has ended’ (p. 1085). A follow-up study of those who completed MCT provides some evidence to suggest the long-term efficacy of the therapy. These patients continued to do well three years later and retained the improvements seen following therapy with 40% returning to work during the intervening period. The fact that some patients were able to return to work provides an outcome of some importance (Thomas & Smith, submitted manuscript).

In conclusion, this body of work has identified a range of factors associated with CFS and factors also that are responsible for influencing the outcome for sufferers of this illness. By adopting the 1991 Guidelines, preliminary investigations into the factors associated with CFS led to the development of methods to better identify this patient group. Continued recruitment allowed more rigorous reporting of these factors using larger patient numbers. As a direct result, measures for subjectively assessing the illness were developed and used to assess recovery and thus describe the natural progression of the untreated illness. Measures of cognitive functioning, developed in studies investigating the effects of factors such as sleep deprivation and colds on human mood.
and performance, were used to identify the impairments associated with CFS and further acted to assess treatment efficacy. Treatment efficacy studies were recommended in two reports commissioned by the Chief Medical Officer (CMO). The rehabilitation courses and counselling services provided by Action for ME offer practical ways to manage symptoms of the illness, thus improving quality of life for the sufferer (and their families). The MCT trial, although limited by small patient numbers, provided an important step towards the alleviation of symptoms both in the short-term and, more crucially, longer-term as well.
6 Limitations of the Body of Work

The results described in Smith, Borysiewicz et al. (1991) and Smith et al (1996) are limited by the relatively small sample of patients investigated – the heterogeneity of the illness indicates that larger participant numbers would be needed to produce more robust findings. Similarly, the MCT trial was also conducted on a very small sample due to the closure of the CFS Clinic and caution is advised when considering the finding’s generalisability.

The Multi Convergent Therapy described in the research comprises several components in an holistic approach to patient care. It would be advantageous to deconstruct the therapy to identify whether it is the holistic nature of the treatment which is instrumental to its success or if the individual parts of it – CBT, graded exercise, mindfulness meditation and so on. – could work as effectively in isolation.

Although investigations into the reporting of Upper Respiratory Tract Infections (URTI) provided interesting preliminary findings, it can be criticised for using subjective self-report measures in its design. As mentioned previously, it might be argued that, in an illness associated with the somatisation of symptoms, these measures were not appropriate. Indeed, further in-depth studies investigating the type of agent responsible for the increased reporting of URTIs were conducted but no novel viral involvement in the patient group were revealed when compared to partner or friend data.

A further limitation of the research was the use of consecutive NHS referrals throughout the project. This method, although recommended in the 1991 Guidelines, was later

14 His element of the Cardiff CFS Project was conducted in collaboration with the Department of Virology, UHW
questioned in terms of its legitimacy as a method of sampling as the resulting sample could be seen to comprise a self-selecting group. That is to say, the group is restricted only to those who sought referral to secondary care and this sub-group may not provide a entirely representative sample of the illness. Future studies using similar measures but this time using a primary care population are, therefore, recommended.

The investigation into the role of antidepressant medication in recovery (Thomas & Smith, 2006) was a retrospective study. It was not possible, therefore, to describe either the dose administered or indeed the duration of treatment using such pharmacological agents. In addition, further analysis has shown that patients who reported recovery at the three year marker were also more likely to be in employment. Employment status was later identified as an important predictor of recovery (Thomas & Smith, submitted manuscript). It could be argued then that a positive change in employment status was in fact responsible for the improvements seen in this sub-sample of patients.
It is often the case that when reporting the findings from research projects one uncovers additional gaps in the literature. The investigation into the deficits associated with CFS has raised questions about the mechanisms behind the reported cognitive impairment. There is a need for further investigations into the neurophysiological changes thought to be associated with CFS as there exists currently a gap in our knowledge as to the nature (and indeed the existence) of these abnormalities. One area of interest is the question of causality – do neurophysiological abnormalities lead to the development of CFS or does a decrease in physical activity – a decrease that is the direct result of the illness itself – then pave the way to such abnormalities developing?

A further point of note is the argument that recruiting patients from a specialised CFS clinic introduces selection bias into the sample and therefore lacks ecological validity. The study of patients recruited from primary care is, therefore, required to address this concern.

Another avenue to explore would be the role antidepressant therapy plays in recovery. For example, recent studies have implicated antidepressant medication in the process of neurogenesis (Duman, 2002) and this may explain the positive outcomes reported in the patient data here reported (Thomas & Smith, 2006). Differences between the Cardiff data and those data collected from other RCTs (Hickie et al., 1999; Natelson et al., 1996; Rimes & Chalder, 2005; Vercoulen et al., 1996; Wearden et al., 1998) need also to be resolved. One possible explanation for the observed difference is that the sub-group in the Cardiff study represents a self-selecting contingent – that is, a sub-sample of patients who have made the decision to take antidepressant medication believing in its efficacy as a course of treatment. Anecdotally, sufferers of the illness report severe negative side-
effects as a result of taking these drugs and decide quickly to discontinue their use. It is possible that those who tolerate antidepressants represent a sub-group of patients who are more likely to recover over time – with or without medication. Further investigations into the optimal time period for antidepressant use in CFS are warranted as are studies looking at the long-term after-effects of taking antidepressants for short periods.

One final area for future research would be further efficacy trials of MCT. One repercussion from the closure of the Cardiff CFS outpatient clinic was a severe limitation on the number of patients successfully recruited on to the study. If a larger trial were to be conducted it would be better placed to occur within primary care. RCTs are currently being criticised for placing too many restrictions on patient inclusion criteria and, in doing so, failing to reflect real world situations - by using rigid inclusion/exclusion criteria for example. It is suggested that further studies into the efficacy of MCT should be conducted in primary care. Furthermore, instead of randomly allocating patients to treatment or placebo groups, each patient should act as their own control. This could be achieved by conducting pre-treatment assessments six-months prior to intervention. It would also be important to explore the individual components of MCT in order to more fully understand its mechanism of action. A recent seminar conducted at the Swansea University School of Medicine has uncovered renewed interest in CFS treatment and it is hoped further collaborations will develop in the near future.

The trial provided another topic for consideration: specifically treatment resistance. Three patients allocated to the MCT group failed to attend their first therapy session. Subsequent letters from the therapist inviting them to re-book an appointment remained unanswered. Investigations into the relatively high attrition rates observed in behaviour therapy trials for CFS are needed to explore this further. Preliminary data suggest that there is a sub-group of patients with poor social problem-solving skills (Christopher &
Thomas, in press). This preliminary finding is not only important in terms of the quite specific social problem-solving deficits associated with the condition, but it has important implications in terms of engaging therapy when offered.

Research into CFS continues to be broadly split into the search for, on the one hand, underlying psychological causes for the condition and, on the other hand, organically-based causes. A growing area of interest in the current research literature is the concept of altered self. When a person suffers an infective insult resulting in activation of the immune system, symptoms such as fatigue, sleep disturbance and impaired concentration also occur. These symptoms are thought to be the result of the body ‘shutting down’ unnecessary systems in order to conserve energy and fight infection (in response to the ‘altered self’). When the infective agent has been eradicated, the body’s immune systems return to their normal resting state. It is thought that in some circumstances the immune system does not return to this state and the body continues to react to the altered self leading to a chronic illness state. It has been suggested that this theoretical model can be adapted to explain the persistent symptoms occurring in CFS, including altered cognition (Jones, 2007).

Investigations also continue in line with the 2002 CMO report which called for the focus of research to return to investigating the aetiology and pathogenesis of the illness. The Cardiff CFS Research Project contributed here also. A team of researchers at Imperial College, headed by Kerr, identified from a pilot study reproducible differences in the expression of sixteen human genes in patients with CFS when compared to healthy controls. Twenty-five sufferers from the Cardiff cohort took part in further investigations made by this team. A paper published as a result of these investigations implicated genes with a variety of functions – immunity and defence, selection regulation,
transcription regulation, translational regulation and G-protein signalling – as being
differentially expressed in CFS patients when compared to the control group (Kerr et al.,
2006). This work is ongoing.
Research into Chronic Fatigue Syndrome and its acceptance by the medical profession has increased a great deal in the past twenty years. That said, its emergence in the medical literature at the close of the nineteenth century, in the first instance as neurasthenia and later Myalgic Encephalomyelitis (ME), has courted controversy. In order to prevent CFS suffering a fate similar to its predecessors – in other words, the lack of a proven aetiology resulting in a loss of scientific interest – an expert panel developed guidelines aimed to assist both clinicians and researchers in the field (Sharpe et al., 1991). Their description of the illness was pivotal to a number of changes in CFS research for two reasons. In this first instance, by providing a coherent description of the illness it was possible to then investigate the possible mechanisms causing the illness. Two pathways were adopted, one focusing on psychological causes, the other physical causes. The second reason is that the research outlined above has improved our understanding of CFS by encouraging the exploration and description of deficits associated with the illness and identifying factors thought to perpetuate it. It went on to utilise the tools developed in the initial stages of the project to successfully measure improvements post-intervention and to evaluate also treatment efficacy. The research has provided a platform from which further, more in-depth studies, can be developed to explore further sub-grouping that exist within the group of patients currently identified as suffering from CFS. It has also identified with success subjective and, more importantly, objective measures by which therapy provision through primary care can be evaluated.

It is hoped that greater understanding of the causal mechanisms in CFS will lead to the development of diagnostic tools and pharmacological interventions. Dr Kerr and his colleagues, for example, are very optimistic about the outcome of their research into gene expression, stating that their: 'comprehensive approach to disease mechanisms in CFS
will soon enable the important process of treatment development (p. 187). Only by continuing to push the boundaries of research can we impact on healthcare policy and practice.

The outlook for sufferers with CFS has greatly improved, both in terms of immediate symptom management and also in terms of the future development of diagnostic tools and long-term treatment opportunities. We may, in the foreseeable future, be able to offer real hope to those who suffer from this disabling and persistent illness.

WORD COUNT (excluding manuscripts) – 11,009
REFERENCES


www.doh.gov.uk/cmo/cfsmereport/index.htm


*British Medical Bulletin, 47*, 815-825.


APPENDICES

Appendix 1: Autobiography of the Candidate

My initial involvement in the research programme was as an assistant to the Project Manager at that time, Dr Pollock (1993-1995), and as such my role was one of data collection, data entry and data collation for the first 67 CFS patients attending the outpatient clinic. Despite my junior role in the early stages of the project I have included the preliminary papers arising from this first cohort of patients (papers 1-3) as these data provide the basis for the methodology used and indeed the rationale behind the research described in the first-author papers.

I was later responsible for the recruiting patients and in addition to data collection, data entry and data collation for the 126 healthy controls described in the ‘abnormal sleep in CFS’ paper (assisted by Ms Perry). These data (patient and controls) were originally stored in a database in DOS format for manipulation and statistical analysis using BMDP – the Bio-Medical Data Processing statistical package (conducted by Professor Smith and Dr Pollock). I subsequently exported these files to SPSS – the Statistical Package for the Social Sciences – and merged them with the second cohort of patients.

Following his appointment to the Department of Experimental Psychology at the University of Bristol in 1995, Professor Smith offered me the opportunity to assume management of the CFS project. One of my first tasks within the larger remit of the project was to conduct an investigation into the effect of Upper Respiratory Tract Infections (URTI) on the symptoms associated with CFS and to assess whether anecdotal reports by patients that they suffer more URTIs than non-sufferers could be
substantiated. Findings from this study are also briefly discussed as an introduction section to the Thesis as they form part of the Linbury Trust proposal.

In order to describe the abnormalities associated with CFS more rigorously it was important to increase the number of patients available through the recruitment panel (see Chapter 3 for more details). I was solely responsible for the recruitment of the second cohort of patients (N=242) as well as being responsible for their assessment and the management of their data. For data management purposes, I created several data-entry programs using Microsoft Access. I later went on to analyse these data.

In parallel to the longitudinal data collection, I designed and conducted a survey to elicit the beliefs and opinions of General Practitioners (GPs) and patients across South Wales. This survey formed part of the Gatsby Foundation proposal which aimed to investigate patient and practitioner education together with the evaluation of possible treatment protocols for CFS. Measuring tools discussed in previous studies conducted by Professor Smith (Smith, 1991; Smith et al., 1993 for example) were developed further in the longitudinal study and subsequently used to assess treatment efficacy in this project.

Studies to explore therapeutic options came in the form of treatment efficacy studies conducted at two research sites: (a) the University Hospital of Wales (Cardiff) and (b) Action for ME (formally Westcare services) in Bristol. Mr Sadlier developed the Multi Convergent Therapy (MCT) described in the trial and conducted the therapy sessions also. I assisted Professor Smith in study design and was solely responsible for coordinating the trial and carried out each patient assessment myself. The Action for ME service evaluation was conducted by postal questionnaire. I was responsible for data collection and data entry, database management and statistical analysis for the trials, the longitudinal study and GP and patient survey. I also prepared ethics submissions for the MCT trial, the GP and patient survey, the Action for ME evaluation and the three-year
MCT follow-up assessment (a small grant from Healthy Minds at Work allowed me to re-evaluate the efficacy of Multi Convergent Therapy over time). Appendix 2 details my contribution to each of the submitted manuscripts together with signed statements from Professor Smith and Professor Sir Borysiewicz – the Principal Investigators for the Cardiff CFS Project – and Mr Sadlier - Director of the MCT Clinic – acknowledging this.
Appendix 2: The Candidates Contribution to the Submitted Manuscripts and Declarations from the Principal Investigators and the MCT Clinic Director

*The Candidates Contribution to the Submitted Manuscripts Compiled by Professor Smith*

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Date: 15/9/08
From the Chief Executive
Sir Leszek Borysiewicz, KBE FRS FRCP FMedSci

10 September 2008

To whom it may concern

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Sir Leszek Borysiewicz  
Chief Executive
To whom it may concern

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**Paper 11:**

<table>
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<tr>
<th>Concept and design</th>
<th>Conduct of research</th>
<th>Analysis of data</th>
<th>Preparation for publication</th>
</tr>
</thead>
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Signature: [Signature]

Date: 24-9-01