

Institution: University of Oxford
Unit of Assessment: 4
Title of case study: <p style="text-align: center;">Development and Demonstration of the First Effective Therapy for Chronic Fatigue Syndrome</p>
1. Summary of the impact <p>Chronic Fatigue Syndrome or CFS (also known as CFS/ME) affects two percent of the population. Michael Sharpe and colleagues in Oxford developed a cognitive behavioural treatment (CBT) for CFS. In 1996 they published the first randomised controlled trial finding that CBT was substantially more effective than standard care, with patients three times more likely to improve. This was the first treatment ever to be shown to be effective for CFS in a clinical trial. The finding was subsequently confirmed in other trials. Sharpe's research has benefitted people with CFS by: [a] challenging the prevailing view of the illness as untreatable, [b] informing current NICE treatment guidance, [c] providing the leading evidence-based treatment. In England alone, the treatment is implemented in 46 NHS specialist CFS centres, to over 7000 patients per year.</p>
2. Underpinning research <p>Chronic Fatigue Syndrome (CFS) is a chronic disabling illness characterised by severe fatigue and other symptoms. Myalgic encephalomyelitis (ME), neurasthenia and post-viral fatigue syndrome are other labels for similar symptoms; it is sometimes referred to as CFS/ME. Since the early 1990s, Sharpe and colleagues have been at the forefront of characterising CFS, and then developing and evaluating the first effective treatment.</p> <p>As recently as the 1980's the condition was widely regarded as untreatable. It also lacked an agreed definition. Having published the first UK research diagnostic criteria for CFS (the 'Oxford definition') in 1991, Sharpe was a co-author on the International (CDC) criteria, which were based on the Oxford definition, and have since been adopted worldwide (Fukuda et al., 1994).</p> <p>Equipped with a reproducible case definition, Sharpe and colleagues in Oxford described the illness related thoughts ('cognitions') and behaviours characteristic of CFS. These findings informed their cognitive behavioural model of the condition, which in turn provided the basis for a new cognitive behavioural treatment (CBT) (Sharpe et al., 1993; Surawy et al., 1995).</p> <p>Arising from these essential initial steps, the key paper is that by Sharpe et al (1996) in the <i>British Medical Journal</i>, which reported a randomised controlled clinical trial, funded by the Wellcome Trust and based in Oxford, in which CFS patients were treated either with CBT or with standard medical care. One year later, 73% of participants who had received CBT reported a substantial reduction in disability, compared with 23% who had received medical care alone; this is a large treatment effect (with a 'number needed to treat' of 4). This seminal paper, the first of its kind, provided critical evidence to challenge the 'untreatable medical illness' view of CFS, and provided the first ever evidence-based treatment for patients suffering from the condition.</p> <p>There have been several subsequent replications of the 1996 Oxford trial. A Cochrane systematic review published in 2009 listed 15 studies, including the original Sharpe et al (1996) trial, and concluded that CBT was an effective treatment for CFS. The most recent and influential replication was the UK-wide MRC funded PACE trial (White et al., 2011) of which Sharpe, then working in Edinburgh, was co-principal investigator; Oxford was a trial centre. Since returning to Oxford in 2011, Sharpe has continued to publish findings from this trial, which underline the value and cost-effectiveness of CBT for CFS (e.g. McCrone et al., 2013).</p>

Contextual Note

Important, independent contributions to research into the psychological treatment of CFS in the 1990s were made by Deale, Chalder, Wessely and colleagues at King's College, London. In 1997, Deale and colleagues published the *second* randomised controlled trial of CBT for CFS (Deale et al., *Am. J. Psychiatry* 1997; 158:408-414). Their study replicated the Sharpe et al. findings reported the previous year.

3. References to the research

Sharpe M. Non-Pharmacological Approaches to Treatment in *CIBA Foundation Symposium 173 - Chronic Fatigue Syndrome* (1993) Editors: Gregory R. Bock, Julie Whelan (pages 298–317) DOI: 10.1002/9780470514382

- *Outlines the cognitive behavioural approach to CFS, and pilot treatment data, as part of the field-defining CIBA Foundation symposium.*

Fukuda K, Straus SE, Hickie IB, **Sharpe M**, Dobbins JG, Komaroff AL (1994) Chronic Fatigue Syndrome: A comprehensive approach to its definition and management. *Annals of Internal Medicine* 121:953-9. DOI:10.7326/0003-4819-121-12-199412150-

- *Based on the work of Sharpe et al ('Oxford definition'). Over 3000 citations.*

Surawy C, Hackmann A, Hawton KE, **Sharpe M** (1995) Chronic fatigue syndrome: a cognitive approach. *Behaviour Research and Therapy* 33, 535-544. DOI: 10.1016/0005-7967(94)00077-W

- *A theoretical paper, elaborating the Oxford cognitive behavioural model of CFS forming the theoretical basis for the Oxford CBT approach. Over 200 citations.*

Sharpe M, Hawton KE, Simkin S, Surawy C, Hackmann A, Klimes I, Peto T, Warrell D, Seagroatt V (1996) Cognitive behaviour therapy for the chronic fatigue syndrome: a randomized controlled trial. *British Medical Journal* 312, 22-26. DOI: doi.org/10.1136/bmj.312.7022.22

- *The key publication, in which the efficacy of CBT for CFS was first demonstrated, in this Wellcome Trust-funded randomised trial. Over 450 citations.*

White P, Goldsmith K, Johnson A, Potts L, Walwyn R, Decesare J, Baber H, Burgess M, Clark L, Cox D, Bavinton J, Angus B, Murphy G, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, **Sharpe M.** (2011) Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet*. 377 823-836. DOI: 10.1016/S0140-6736(11)60096-2

- *The MRC-funded PACE trial which cited Sharpe's trial and replicated the effect of CBT in CFS. Sharpe was a principal investigator (together with White and Chalder). Over 130 citations.*

McCrone P, **Sharpe M**, Chalder T, Knapp M, Johnson AL, Goldsmith KA, White PD (2012) Adaptive pacing, cognitive behaviour therapy, graded exercise, and specialist medical care for chronic fatigue syndrome: A cost-effectiveness analysis. *PLoS One* 7, e40808. DOI: 10.1371/journal.pone.0040808

- *Demonstrated that CBT is the most cost-effective of the current treatments for CFS, and that CBT is the only treatment to reduce the societal burden.*

Underpinning grants:

1992-5 Wellcome Trust (£200,000): Principal Applicant, Cognitive therapy for patients with chronic fatigue syndrome: a randomised trial.

- 1994-7 Linbury Trust (£150,000): Principal Applicant, Studies of chronic fatigue syndrome.
- 2004-11 MRC (£5 million) Co-principal Applicant (with White and Chalder, London): PACE trial.

The underpinning research took place while Sharpe was Clinical Tutor in Psychiatry in Oxford. Key colleagues included Keith Hawton, Sue Simkin, Ann Hackmann and Christine Surawy.

4. Details of the impact

This Oxford based research has had a positive impact on people with CFS in three important ways. It has: [a] changed how the illness is viewed, from untreatable to treatable; [b] provided an evidence-based treatment that is recommended in current NICE and other guidelines; and [c] has become a standard treatment delivered through NHS CFS/ME treatment centres.

[a] Changed view of the illness

A key impact of this research has been to change professional and public views of the illness (Section 5, Sources 1-3). Previously regarded as an untreatable medical condition best treated by rest, CFS/ME is now seen by most informed professionals and patients as an at least partially reversible illness which can be treated with the type of CBT developed in Oxford. The new idea of an effective treatment was recognised in medical review articles as early as 1998 (see Levine, Source 1). The resulting change in the public understanding is evidenced in a House of Lords debate in February 2013, in which one peer espoused the old view that CFS/ME was an untreatable condition, whereas all seven other peers who spoke disagreed, and spoke in support in the benefits of CBT (see Hansard, Source 2).

[b] Influence on clinical guidelines

The second impact has been on clinical guidelines (see Sources 4-7). The current guideline for the treatment of CFS/ME in the UK (written by the National Institute for Health and Clinical Excellence, NICE) was published in 2007. This guideline identified CBT as the most effective evidence-based treatment for patients with CFS. The NICE guideline was based on a systematic review conducted by the Centre for NHS reviews and dissemination at York University, which specifically cites the original Oxford trial by Sharpe et al. (1996).

[c] A standard, and cost-effective, evidence-based treatment

CBT has become a standard treatment for CFS. If two percent of the UK population have CFS (as has been estimated), then more than a million people suffer from the condition. As the number need to treat (NNT) in the 2009 Cochrane review of trials of CBT for CFS was 7 (using a conservative estimate), well over 100,000 patients hypothetically could benefit from this treatment. In practice, there are specialist NHS treatment centres for CFS (49 in England, 46 of which provide CBT). These centres treat over 7,000 patients per year (Collin et al., 2012; Source 8), meaning that *over 1,000 patients with CFS in England can be expected to benefit substantially from CBT each year*. This benefit has been confirmed by a national audit (Crawley et al., 2013; Source 9). These numbers do not take account of the many patients treated outside these centres in England, nor in the rest of the UK and in other countries.

Subsequent research by Sharpe and colleagues has found that CBT is *cost-effective* for CFS, and also leads to a reduction in the burden placed on family members caring for a patient with CFS (see McCrone et al., 2012; cited in section 3 above).

CBT is also recommended for CFS by the Centres for Disease Control in the USA (Source 10).

The impact of this work has spread beyond CFS, and has influenced the conceptualisation and treatment of fatigue in other conditions such as multiple sclerosis (Van Kessel et al., *Psychosomatic Medicine* 2008; 70:205-213).

5. Sources to corroborate the impact

[a] Changed views about the illness

1. "Although at the present time there is no "magic bullet" treatment for CFS and the principles of management continue to rely on the treatment of symptoms as they arise, the continuing development of information pointing to a role of the central nervous system provides a *rationale for the use of cognitive behavioral therapy, which has been shown to be effective by Sharpe and others.*" P. Levine, *American Journal of Medicine*, 1998: **105(3A)**:100S-103S.

Impact case study (REF3b)

2. The Hansard text of a recent debate in the House of Lords. [NB: the # symbol in URL may need to be re-typed]:
<http://www.publications.parliament.uk/pa/ld201213/ldhansrd/text/130206-gc0001.htm#130206114000184>

3. The benefit of CBT and the Sharpe trial are referenced in Wikipedia:
http://en.wikipedia.org/wiki/Chronic_fatigue_syndrome_treatment

[b] NICE guidance

4. The current 2007 NICE guidelines on the management of CFS have been influential in informing the treatment given in centres around the UK. (see below)
(<http://guidance.nice.org.uk/CG53> "*Cognitive behavioural therapy is effective in adults and has been shown to reduce symptoms, improve function and improve quality of life (Evidence level 1+)*". [i.e. a very high level of evidence].

5. Similar findings are reached by a 2010 clinical evidence review:
<http://clinicalevidence.bmj.com/x/pdf/clinical-evidence/en-gb/systematic-review/1101.pdf>

6. CBT is recommended for CFS on NHS Choices <http://www.nhs.uk/Conditions/Chronic-fatigue-syndrome/Pages/Treatment.aspx>

7. BACME is the UK organization for clinicians treating patients with CFS. It links the NHS treatment centres. The organizations aim is to "champion evidence-based approaches to the treatment of CFS/ME, such as those provided in the NICE guidelines." The information page states: "*Cognitive behaviour therapy (CBT) is a treatment that has been found to be effective in helping people with chronic fatigue syndrome (CFS)*". The information page also provides a map of services around the UK, most of which provide CBT for patients with CFS/ME.
<http://www.bacme.info/aboutbacme/>

[c] Standard treatment

8. Survey data finding that approximately 7000 patients are treated by the 49 NHS specialist CFS/ME treatment services in England alone: Collin et al. 2012, *BMJ Open*:
<http://bmjopen.bmj.com/content/2/4/e001417.full?sid=6a7f1fd0-26db-484f-9527-00ad1897772e>

9. Audit data from services reporting substantial clinical improvement with a NNT approximately 7, and improvement in fatigue with a much lower NNT: Crawley et al, 2013, *Quarterly Journal of Medicine*: <http://qjmed.oxfordjournals.org/content/early/2013/03/28/qjmed.hct061.abstract>

10. The Centres for Disease Control in the USA recommend CBT for CFS, and it is a key component in their 'toolkit' <http://www.cdc.gov/cfs/toolkit/cbt.html>