



Adverse events and deterioration reported by participants in the PACE trial of therapies for chronic fatigue syndrome



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ARTICLE INFO

Article history:

Received 22 November 2013

received in revised form 31 March 2014

accepted 8 April 2014

Keywords:

Adverse events

Body mass index

Chronic fatigue syndrome

Depression

Medically unexplained symptoms

ABSTRACT

Objective: Adverse events (AEs) are health related events, reported by participants in clinical trials. We describe AEs in the PACE trial of treatments for chronic fatigue syndrome (CFS) and baseline characteristics associated with them.

Methods: AEs were recorded on three occasions over one year in 641 participants. We compared the numbers and nature of AEs between treatment arms of specialist medical care (SMC) alone, or SMC supplemented by adaptive pacing therapy (APT), cognitive behaviour therapy (CBT) or graded exercise therapy (GET). We examined associations with baseline measures by binary logistic regression analyses, and compared the proportions of participants who deteriorated by clinically important amounts.

Results: Serious adverse events and reactions were infrequent. Non-serious adverse events were common; the median (quartiles) number was 4 (2, 8) per participant, with no significant differences between treatments ($P = .47$). A greater number of NSAEs were associated with recruitment centre, and baseline physical symptom count, body mass index, and depressive disorder. Physical function deteriorated in 39 (25%) participants after APT, 15 (9%) after CBT, 18 (11%) after GET, and 28 (18%) after SMC ($P < .001$), with no significant differences in worsening fatigue.

Conclusions: The numbers of adverse events did not differ significantly between trial treatments, but physical deterioration occurred most often after APT. The reporting of non-serious adverse events may reflect the nature of the illness rather than the effect of treatments. Differences between centres suggest that both standardisation of ascertainment methods and training are important when collecting adverse event data.

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Introduction

Clinical trials frequently attribute health problems that arise during a trial to the intervention. But, when health problems typically remit and relapse, the attribution of all new health problems to the intervention may be misleading. This study aims to explore this issue in patients with chronic fatigue syndrome (CFS) who participated in a treatment trial.

Adverse events reported by participants in clinical trials of treatments may be considered to be clinically serious or not, and to

be reactions to trial treatments or not. Few studies have examined the associations and predictions of adverse events in trials. Several trials have suggested a relationship between the reporting of adverse events and negative affect; anxiety [1], depression [2] and neuroticism [3]. Females and introverted participants of phase 1 medical trials are more likely to report adverse events than males and extroverts [4]. Physical symptoms at baseline predicted having a treatment related adverse reaction in an antidepressant controlled trial [5]. As well as this small literature regarding adverse events in trials, there are well established associations between reporting physical symptoms, outside of trials, and both mood disorders [6–10] and symptom burden [11].

Chronic fatigue syndrome (CFS) is characterised by long-standing disabling fatigue and other symptoms that have no alternative medical or psychiatric explanation [12]. Its nosological status and aetiology are

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uncertain [13]. CFS is associated with functional somatic syndromes such as irritable bowel syndrome and fibromyalgia [14]. Treatments recommended by the National Institute of Healthcare and Clinical Excellence (NICE) include cognitive behaviour therapy (CBT) and graded exercise therapy (GET) [15], but patient organisations have expressed concern about their efficacy and safety [16].

The PACE trial was a four arm randomised trial, which was designed to compare three therapies each added to specialist medical care (SMC) against SMC alone to determine both efficacy and safety [17]. The trial found that two therapies, CBT and GET, were more effective than adaptive pacing therapy (APT), when any of these therapies were added to SMC, and were more effective than SMC alone [17]. Whilst CBT and GET were designed to be rehabilitative, the goal of APT was to optimise adaptation to the illness by planning and pacing activities to avoid or reduce fatigue [17]. The trial measures of safety included systematic assessments of adverse events (AEs), which occur uncommonly in trials of behavioural interventions [18]. We have already reported that there were few serious adverse events (SAEs) and even fewer serious adverse reactions (SARs), the numbers of which did not differ significantly across treatment arms [17]. We have also reported various measures of deterioration, but not whether there are any differences across treatment arms in the proportions of participants who deteriorated in the two primary outcomes by a clinically important amount [17]. This paper reports the more commonly reported non-serious adverse events (NSAEs), compares their frequency between treatment arms, and also identifies baseline factors associated with reporting larger numbers of NSAEs [17,19]. On the basis of the previous literature, we hypothesised that NSAEs would be associated with female sex, a larger number of physical symptoms at baseline, and both depressive and anxiety disorders present at baseline. To our knowledge there has been no previous study examining associations of NSAEs in a trial of treatments for CFS or functional somatic syndromes.

Methods

Outline of the PACE trial

This report uses data from the PACE trial, relevant aspects of which are described; more comprehensive accounts are available in the protocol [19], and the primary paper [17]. The PACE trial recruited 641 patients from secondary care clinics with a diagnosis of CFS, using the Oxford criteria, which require six or more months of disabling fatigue, with fatigue being the principal symptom, and no alternative, explanatory diagnosis [20]. Participants were randomly allocated to one of four treatment arms consisting of specialist medical care (SMC) alone or SMC with one of APT, CBT or GET. Randomisation to the four treatment arms was stratified by centre, co-morbid depressive disorder, and different CFS and myalgic encephalomyelitis (ME) criteria [12,21]. Following randomisation, participants received up to 15 sessions of therapy (if allocated to a therapy arm) and at least 3 sessions of SMC.

All consecutive new outpatients from six secondary care CFS clinics in England and Scotland with a clinical diagnosis of CFS were clinically assessed for eligibility and, if they agreed, were screened by a research assistant (RA) for eligibility and consent for the trial. RAs were either nurses or psychologists, who were independent of clinical staff, but were not masked to treatment arms, this being impractical to achieve. There was only one RA per centre, but over the trial period, RAs left and were replaced in some centres. Recruitment commenced in March 2005 and was completed by Nov 2008. Follow-up was up to one year from randomisation.

Inclusion criteria were meeting the Oxford research diagnostic criteria for CFS [20], a Chalder Fatigue Questionnaire binary score of 6 or more [22], a SF36 physical function sub-scale score of 65 or less [23] and age at least 18 years old. Exclusion criteria were a significant risk of self-harm, being considered by the RA to be unable to participate in the trial, participation in the PACE trial being inappropriate for clinical

needs, and patients who had previously attended a PACE centre specialist fatigue clinic and received a course of PACE trial consistent treatment [19].

The Structured Clinical Interview for DSM-IV was administered by the RA, after appropriate training, and used to assess psychiatric comorbidity and psychiatric exclusions [24]. Further baseline information collected included demographic details, current membership of a local or national ME self-help group, and body mass index (BMI). Additional self-report questionnaires included the Chronic Disease Self-Efficacy measure [25], physical symptoms (Patient Health Questionnaire; PHQ-15) [26], Cognitive Behavioural Responses Questionnaire (CBRQ) [27], Jenkins sleep scale of subjective sleep problems [28], and the Hospital Anxiety and Depression Scale (HADS) [29]. Further assessments consisted of the International (CDC) criteria for CFS [12], the London criteria for myalgic encephalomyelitis [21] and the presence or absence of fibromyalgia [30].

Assessment of adverse events

Follow-up assessment interviews were conducted by the RA at each centre on three occasions: 12, 24 and 52 weeks after randomisation. At each of these time points the RA asked participants whether any new events or illnesses had taken place since the last assessment including any events for which the participant visited the GP or hospital department, or took medication [19]. AEs were also recorded by treating specialist doctors and therapists if spontaneously reported to them during the trial. An AE was defined as 'any clinical change, disease or disorder experienced by the participant during their participation in the trial, whether or not considered related to the use of treatments being studied in the trial' [19]. We did not examine inter-rater reliability between RAs since we did not foresee variability in these assessments.

AEs included: (a) any new co-morbid medical conditions reported, if not previously reported at baseline, (b) any events for which the participant consulted their GP or other medical advisor or took medication, and (c) any other events that might have affected the health status of the participant (e.g. increased work stress). Examples of NSAEs included a cold (which had not caused serious disability), an eye infection, or the experience of new pain (if not previously reported as a symptom of the participant's CFS). If in doubt, the RA was encouraged to contact the GP for both an update of all visits to the surgery since the last research session and a list of any medications prescribed. The RA also took note of any new events recorded in the clinic notes by the SMC doctor at these sessions or reports thereof from the treating specialist doctor or therapist.

Two consultant physicians and a consultant liaison psychiatrist, all experienced in CFS, were appointed as independent scrutineers and were masked to the participants' allocated treatment group. They determined whether each AE was serious or non-serious. A serious adverse event (SAE) was an event that resulted in one of the following outcomes: a) death, b) threat to life (i.e., an immediate, not hypothetical, risk of death at the time of the event), c) required hospitalisation except for elective treatment of a pre-existing condition, d) increased severity and persistent disability, defined as: (i) severe, i.e. significant deterioration in the participant's ability to carry out their important activities of daily living (e.g. employed person no longer able to work, caregiver no longer able to give care, ambulant participant becoming bed bound); and (ii) symptom and disability persistent, i.e. of at least 4 weeks continuous duration, e) any other important medical condition which, though not included in the above, might require medical or surgical intervention to prevent one of the outcomes listed, and f) any episode of deliberate self-harm. For any AE established as serious, the scrutineers were unmasked to treatment allocation to establish whether or not the event was a serious adverse reaction (SAR). A serious adverse reaction was considered to be a reaction to one of the supplementary therapies or a drug prescribed as part of SMC [19]. All those

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