ARTICLE

Medically unexplained syndromes: irritable bowel syndrome, fibromyalgia and chronic fatigue

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SUMMARY

This is a review of three of the more common medically unexplained syndromes that present for treatment to liaison psychiatry services in general medical hospitals: chronic fatigue syndrome, fibromyalgia and irritable bowel syndrome. The three are interrelated, extremely disabling and comorbid mood disorders are frequent. In general, treatment, whether psychological or medical, has very modest impact. The disputed classification of medically unexplained syndromes is also reviewed. There is a clear gulf between the views and experiences of patients with these syndromes and the medical establishment. In this article I summarise give the evidence for pharmacological, psychosocial and 'alternative' or 'complementary' interventions for a range of disorders, about which there is some dispute. I leave it to the reader to decide which interventions hold the most promise.

LEARNING OBJECTIVES

- To become aware of the high prevalence of medically unexplained syndromes
- To review the effectiveness of treatment of medically unexplained syndromes
- To be familiar with the conflict between health professionals and patients and the difficulty this continues to create

DECLARATION OF INTEREST

None.

In this article I describe some of the more common medically unexplained syndromes that present for treatment to liaison psychiatry services in general medical hospitals: irritable bowel syndrome (IBS), fibromyalgia and chronic fatigue syndrome (CFS). These syndromes have considerable overlap in symptoms, such that many experts do not distinguish between CFS and fibromyalgia.

Medically unexplained syndromes are common. The prevalence of fatigue symptoms in the community ranges from 5 to 20%, although the prevalence of strictly defined CFS is estimated at 0.2–2.6% (Prins 2006). Fibromyalgia is the third most common rheumatic disorder after low back pain and osteoarthritis, affecting 2–8% of the general population (Branco 2010). Estimates suggest that between 10 and 15% of adults suffer IBS and it accounts for 25% of gastroenterology consultations (Chey 2015).

These syndromes are notoriously persistent and difficult to treat, and although they are not terminal (life expectancy is usually normal) they are very disabling. CFS is often irreversible: only 1 in 20 patients recovers completely and, although half show some improvement, one-third remain disabled (Cairns 2005). Only 10–30% of individuals with CFS return to work. Similarly, fibromyalgia does not reduce life expectancy, but it is very disabling and around half of patients have great difficulty with activities of daily living. It is estimated that 30–40% of people with fibromyalgia have to change or stop work (Arnold 2011; Simon 2012).

The majority of patients with these syndromes have had several frustrating years of extensive and intrusive investigations by multiple, often bemused, medical specialists with little or no benefit, thereafter to be told that they should see a psychiatrist – with the implication that there is nothing physically wrong with them. Managing expectations by making reasonable estimates of the likely improvement is therefore a sensible strategy and all patients need to be reassured that their symptoms are not assumed to be psychological and that they are indeed experiencing the symptoms they describe. Some useful treatment boundaries and expectations advised by Paiva & Jones (2010) for fibromyalgia are equally sensible when treating any patient with an unexplained medical syndrome. These include specifying both the frequency and duration of clinic visits and the availability, or otherwise, of out-of-hours and therapist contact between appointments, prioritising reasonable treatment goals, and explaining the long-term outcome and prognosis.

The classification of somatic symptom disorder

Psychogenic (psychosomatic) symptoms are thought to be produced by psychological (mental) rather than physical (somatic, organic or bodily)

processes. Psychogenic disorders may be better called 'functional', as this does not presume any particular cause, physical or psychological (Benbadis 2005). 'Somatic symptom disorder' is the latest diagnostic term used by DSM-5, sitting in the category 'somatic symptom and related disorders', and it replaces 'somatisation disorder' (American Psychiatric Association 2015).

The terms 'physical' or 'organic' disorder imply that there is some abnormality on objective clinical tests such as blood tests, electroencephalogram (EEG) or magnetic resonance imaging (MRI) scans, or simply that medical specialists have a consensus that there is a physical cause (such as trigeminal neuralgia). The term 'medically unexplained syndrome' is used to categorise collections of signs and symptoms that leave doctors perplexed. Estimates suggest that 10% of medical consultations are for medically unexplained or 'functional' symptoms (den Boeft 2017). Many of these are pain syndromes that are referred to pain specialists.

Although each medical specialty has identified certain functional syndromes, psychiatrists are increasingly involved in the management of some of the more common intractable and disabling medically unexplained syndromes such as fibromyalgia, chronic fatigue and IBS (Baslet 2012). As mentioned above, there is great overlap between these three syndromes, with many patients suffering from more than one of them. It remains a matter of dispute as to whether these syndromes should be 'lumped' together as a common disorder or whether they should be 'split' into separate diagnostic entities (Aaron 2001; Baslet 2012).

'True' functional disorders should be distinguished from factitious disorders and malingering, in both of which the patient is thought to be deliberately (consciously) simulating symptoms (World Health Organization 2010; American Psychiatric Association 2015). There are usually obvious advantages to seeking the sick role in malingering (such as claiming compensation or benefits, obtaining drugs, or evading work, criminal responsibility or military service). By contrast, the motivation for simulating symptoms in 'factitious disorders' is usually obscure and often impossible to identify. Hence, it is only by catching a patient simulating symptoms (such as deliberately catheterising or self-harming) or by covertly observing normal behaviour (such as walking unassisted) that fictitious disorders are identified (Reubera 2003; Benbadis 2005; Baslet 2012).

To add further confusion, the subclassifications of medically unexplained symptoms are changeable and remain highly controversial (den Boeft 2017). 'Somatisation' disorders are characterised by preoccupations with multiple medically unexplained bodily symptoms (over at least 2 years). 'Hypochondriasis' is a preoccupation with the presence of a presumed undiagnosed serious illness, which leads to excessive requests for reassurance and medical investigations despite multiple negative results. ICD-10 (World Health Organization 2010) classifies these disorders as 'somatoform disorders'. 'Somatoform autonomic dysfunction', 'persistent somatoform pain disorder' and 'neurasthenia' (chronic fatigue) are further subclassifications. There is also a group of 'dissociative (conversion) disorders', in which symptoms such as amnesia, loss of bodily function or sensation, or impaired consciousness occur without sufficient organic cause. These dissociative disorders (previously classified as forms of 'conversion hysteria') are presumed to arise as a result of a traumatic event with a psychoanalytic or 'unconscious' mechanism, at least according to the definition. The patient may have no memory of the event – according to psychoanalytic theory it has been 'repressed'.

There is now a move away from the presumption of unconscious mechanisms and DSM-5 does not make any assumptions about psychodynamic cause in its classification of 'somatic symptom disorder' (American Psychiatric Association 2015). Somatisation disorders have a prevalence of between 0.2 and 2%, with higher rates in women than men (Baumeister 2007).

ICD-11 (expected to be published in 2018) has lost the diagnosis of hypochondriasis. However, 'health anxiety' and 'bodily stress syndrome' have been introduced. The latter includes unexplained medical symptoms that are not associated with disproportionate anxiety – for example palpitations, abdominal pain or movement and sensory disorders. These may be due to autonomic arousal or the autonomic nervous system or the 'reticular formation' – there is an implicit suggestion that they may have a neurological cause (Lam 2013).

Comorbid mood disorders in medically unexplained syndromes

Depression and anxiety are common in chronic fatigue. For example, between 18 and 39% of participants in two trials of CFS reported comorbid depression (cited in Wearden 2010). In large surveys 25% of people with chronic fatigue meet criteria for 'major depression' and around 75% have a life-time diagnosis of depression (Skapinakis 2000). Similarly, anxiety and depression are common in people with chronic fatigue, with prevalence rates of 42.2 and 33.3% respectively (Daniels 2017).

Epidemiological studies report that individuals with fibromyalgia have a high lifetime prevalence of depressive and anxiety disorders (Epstein1999).

Many studies did not distinguish between chronic fatigue and fibromyalgia, as patients met criteria for both disorders. Depression is reported to occur in around 40% (although estimates vary from 20 to 80%) of people with fibromyalgia (Thieme 2004; Kurland 2006; Fietta 2007; Aguglia 2010). This compares with rates of depression estimated at 8% for other patients attending rheumatology clinics (Kurland 2006). The most common disorders were major depression (lifetime prevalence 68%, point prevalence 22%), dysthymia (point prevalence 10%), panic disorder (lifetime prevalence 16%, point prevalence 7%) and simple phobia (lifetime prevalence 16%, point prevalence 12%) (Epstein1999). Around 1.3% of US adults will have persistent depressive disorder (dysthymia) in their lifetime based on the National Comorbidity Survey Replication (NCS-R) study (Harvard Medical School 2007).

Depression and anxiety disorders are reported in 20–30% of people with IBS (Kabra 2013). In one study 32% of individuals with the syndrome reported general anxiety disorder symptoms (Fadgyas-Stanculete 2014). Another study reported that the majority of African American women with IBS suffered moderate to severe depression (73%) and 17.3% had severe depression (95% CI, 7.3–35.5), although high rates of comorbid alcohol misuse may have confounded this result (Iorio 2014).

Post-traumatic stress disorder (PTSD) is increasingly recognised in patients with medically unexplained syndromes. For example, one study reported that 57% of patients with fibromyalgia also met criteria for PTSD (Cohen 2002). These findings are supported by other studies suggesting that just over 50% of fibromyalgia patients reported PTSD-like symptoms (Sherman 2000). By contrast, 7.8% of patients with IBS met the diagnostic criteria for PTSD (Cohen 2006). Another study reported that 36% of patients with IBS met criteria for lifetime PTSD (White 2010).

Irritable bowel syndrome

Clinical features

Irritable bowel syndrome (IBS) is a recurrent relapsing condition, with no abnormalities on routine medical tests. It is characterised by episodes of abdominal pain and perceived changes in bowel habit (both diarrhoea and/or constipation) on 3 or more days a month for more than 3 months (Chey 2015). Blood in the stools is common in IBS, reported by around one-third of patients, although it may also be related to concurrent haemorrhoids. There is a significant overlap in IBS symptoms with those of other medically unexplained syndromes, especially fibromyalgia and chronic fatigue (Aaron 2001). A large survey of almost 100 000 individuals with IBS suggested that the symptoms of IBS occurs in around half of patients with CFS or fibromyalgia (Cole 2006).

IBS is a familial condition. IBS does not reduce life-expectancy. An acute gastrointestinal infection increases the risk of developing IBS sixfold. Abuse and sexual trauma are also reported in around one-third of women with IBS (Sansone 2015).

IBS is a diagnosis of exclusion – there are no diagnostic tests. Patients will usually be screened for other disorders, such as coeliac disease (gluten intolerance), parasitic infections (e.g. giardiasis), thyroid disease and occasionally carcinoid syndrome. Many patients will also be investigated for carcinoma of the bowel and inflammatory bowel disease (ulcerative colitis and Crohn's disease) by endoscopy, colonoscopy and abdominal ultrasound. Hydrogen breath testing may be used to exclude intestinal bacterial overgrowth and malabsorption of fermentable sugars (fructose and lactose).

Prevalence

Estimates suggest that between 10 and 15% of adults throughout the world suffer IBS, and IBS has been estimated to account for 25% of gastroenterology consultations (Chey 2015). IBS is twice as common in women than in men and usually develops before middle age.

Management

A Cochrane review has shown that laxatives (buling agents) antispasmodics and antidepressants are often used to treat IBS although evidence for their effectiveness is weak (Ruepert 2011).

Drugs that inhibit serotonin function, such as the anti-emetic ondansetron, are useful in IBS (Talley 2001). Olanzapine and clozapine may also reduce symptoms, possibly by their inhibitory action at serotonin receptors (Pae 2013). Amitriptyline and other tricyclic antidepressants have been widely used in IBS. One meta-analysis gave a number needed to treat (NNT) of 3 for tricyclic antidepressants in IBS (Jackson 2000). Paradoxically, selective serotonin reuptake inhibitors (SSRIs) may worsen IBS symptoms by promoting serotonin, which increases bowel motility, although they may improve mood symptoms (Creed 2005; Turner 2008; Xie 2015).

Cognitive–behavioural therapy (CBT) and hypnosis have been used in IBS, although the formal evidence for effectiveness is weak and psychological measures are recommended only after 12 months of conventional physical treatment (National Institute for Health and Care Excellence 2008).

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A meta-analysis of 18 randomised trials of CBT in IBS showed some benefit in reducing symptoms, although CBT was no better than other psychological approaches (Li 2014). A reasonable effect size of 0.68 was reported for overall improvement at post-treatment follow-up (effect size of 0.49 for quality of life).

Some reports indicate that IBS symptoms improve using a 'low-FODMAP' diet, with reduced fermentable sugars (Staudacher 2014). Yoga, probiotic bacteria and acupuncture are also commonly used non-hazardous treatments, although they are seldom subject to rigorous trials and scrutiny (Brandt 2009). Dietary interventions for IBS are considered in Box 1.

Fibromyalgia

Clinical features

Fibromyalgia is a chronic disorder involving pain for at least 3 months in multiple joints in each of the four quadrants of the body, without an organic explanation on routine clinical tests. Symptoms also include sleep disturbance, muscle pain, hypersensitivity to pressure, touch, noise and light, restless legs syndrome, bowel and bladder problems, chronic tiredness, numbness and paraesthesia ('pins and needles') (Arnold 2012). Atypical facial pain and pain in the temporomandibular joint are also common.

There is no diagnostic test for fibromyalgia. Many patients present initially to rheumatologists and are screened for autoimmune and other inflammatory disorders. There is considerable overlap between fibromyalgia and CFS and many of the routine laboratory tests are common for investigation of both disorders (these are listed below, in the section on CFS).

Prevalence

The overall prevalence of fibromyalgia is between 2 and 8% of the population and rates are similar worldwide (Branco 2010). Women are affected twice as often as men. Fibromyalgia is more common in relatives of sufferers. Fibromyalgia is the third most common rheumatic disorder after low back pain and osteoarthritis.

BOX 1 Irritable bowel syndrome and diet

Over 80% of people with irritable bowel syndrome (IBS) report their symptoms are aggravated by at least one food item, and almost 70% report that changing their diet improved symptoms (Simren 2001; Monsbakken 2006). Various theories suggest that IBS may be due to an immunological response or to luminal distention (swelling of the bowel) by foods that attract water by osmosis or produce gas. One theory is that IBS is caused by the release of serotonin or histamine from gut mast cells (Wouters 2015). There is also some more recent evidence that the intestines of people with IBS are more sensitive than those of controls, especially to distention produced by gas or fluid intrusion (Keszthelyi 2014). The nervous system within the gut may be overreacting to normal changes in the digestive processes or normal stimuli. This leads to pain, diarrhoea or constipation (Camilleri 2012).

Evidence for the therapeutic effect of increasing dietary fibre (bulking agents such as ispaghula) is equivocal: a Cochrane review of 12 trials reported no benefit (Ruepert 2011) and another meta-analysis found minimal improvement (Ford 2008).

A randomised controlled trial (RCT) involving 179 individuals with IBS comparing a probiotic *v.* non-probiotic dairy product was reviewed over 12 weeks (Roberts 2013): 46% of participants receiving active treatment (probiotic yogurt) reported significant relief *v.* 68% receiving placebo at 8 and 12 weeks (assessed by several measures, including IBS symptom severity scores). This showed no advantage of probiotic diets.

Trials have also attempted to modify diets to remove gas-producing foods which may cause distention of the intestine, such as wheat germ, beans, cabbage, bananas, prunes, Brussel sprouts and onions (Portincasa 2017). These include 'low-FODMAP' diets that reduce fermentable oligosaccharides, disaccharides, monosaccharides and polyols – these are compounds that resist digestion and produce gas and water influx (Shepherd 2013).

The acronym FODMAP was devised in 2005 by Gibson & Shepherd at Monash University in Melbourne (Catassi 2017). The most recent guidelines from the British Dietetic Association recommend low-FODMAP diets as second-line treatment of IBS (McKenzie 2016). A trial of a low-FODMAP diet and traditional IBS diet (which also excludes many FODMAP constituents) involving 74 participants over 4 weeks showed that the IBS Symptom Severity Scale scores halved (taken to be clinically significant) in 46–50% of the treatment group compared with base-line scores (Böhn 2015).

A meta-analysis of 6 randomised and 16 non-randomised trials of low-FODMAP diets in IBS reported a significant improvement with the low-FODMAP diet – the pooled odds ratio for improvement in the randomised trials (0.44) was highly significant, the outcomes usually being based on the ISB symptom severity scores (Marsh 2016).

Lactose, fructose, gluten and sucrose intolerance have also been considered and diets have recently been studied in small trials that exclude these substances (Portincasa 2017). The results of these trials are equivocal. However, a double-blind RCT of gluten challenge concluded that 'non-coeliac gluten intolerance' might exist. The trial involved 34 individuals with IBS who did not have coeliac disease and who were all complying with gluten-excluding diets. Over 6 weeks the participants received either gluten or placebo. IBS symptoms were not adequately controlled in 68% of the gluten-challenged group, compared with 40% of the placebo group (Biesiekierski 2011).

Overall, it is clear that dietary modification can improve symptoms in IBS, although it remains to be determined which constituents need to be excluded from the diet to show improvements. Similarly, it remains uncertain whether the improvements in symptoms are due to an immunological response to food constituents or a physiological response to bowel dilation due to gas production or osmotic intrusion of water. The mechanism of action is significant, as bowel dilation (luminal distention) could produce symptoms by centrally mediated sensory hyperactivity responses rather than by a direct action on the bowel wall – the disturbance may be in processing within the central nervous system rather than within the bowel itself.

Management

Combinations of psychosocial treatment are usually recommended in fibromyalgia. A meta-analysis of 'multicomponent' treatment reviewed 9 randomised trials with nearly 1119 patients (Häuser 2009). The study reported a modest reduction in pain (standardised mean difference SMD = –0.37) and larger improvements (SMD = 0.6–0.8) in fatigue, depressive symptoms, physical fitness and quality of life. The scores were determined at the end of each treatment episode.

A large meta-analysis of 102 trials (14 982 participants) of medication and psychosocial treatment for fibromyalgia reported small benefits for pregabalin and multicomponent therapy, although the analysis was restricted to larger trials and their quality was low (Nüesch 2013).

Non-pharmacological treatment of fibromyalgia includes techniques such as CBT (Box 2), graded exercise exposure (also known as graded exercise therapy) and various forms of psychoeducation (such as sleep hygiene). The overall effect sizes tend to be small, with trials usually being small and difficult to perform (Glombiewski 2010). CBT and graded exercise exposure are used widely in treatment of both chronic fatigue and fibromyalgia. Sleep hygiene if often a technique used in CBT.

Graded exercise exposure/therapy

Graded exercise exposure involves increasing modest activity (such as walking) typically by 10 min per day and escalating to between 30 and 60 min of moderate activity around 3 times per week. The general advice is 'start low, go slow' (Fulcher 1997; Arnold 2012). If exercise produces adverse symptoms then the individual should reduce the exercise temporarily until the symptoms resolve. Box 3 outlines National Institute for Health and Care (NICE) guidance on graded exercise therapy.

A Cochrane review of fibromyalgia treatment suggests that a 12- to 24-week graded exercise programme (20 min a day of stepping or walking, 2–3 times per week) leads to a modest improvement in overall well-being (7% absolute improvement compared with controls; SMD = 0.49) and improvement in pain scores, although it is unclear whether this improvement in pain was clinically significant (13% absolute improvement; SMD = 0.65) (Busch 2007). The overall results are based on 2276 participants in 34 trials. The effects on physical functioning are uncertain. It is likely that the exercise programme must continue indefinitely to observe continued benefit. Unfortunately, there is a high drop-out rate for long-term exercise programmes. It was reported that 'strength training' (8–12 repetitions of weight training or similar exercise, 2–3 times per week) produced a 50% reduction in pain and 41% absolute improvement in well-being, although only one study was of moderate quality and three were small (Busch 2007).

A Cochrane review of weight training ('resistance training' typically 2–3 times per week for 6 months) reported on 5 trials involving 219 women (Busch 2013). The training group rated that their well-being improved by 25 points on the 100-point scale, compared with an 8-point improvement in the control group (a 17% absolute improvement). The training group rated that their pain improved by 3.5 points on a 10-point scale, compared with a 1-point improvement in the control group (a 25% absolute improvement).

Another Cochrane review of 'aquatic exercise training' in 16 studies with 866 women reported that those who did the exercise rated that their pain or well-being improved by between 6 and 7 points more than the controls on a 100-point scale (a 6–7% absolute improvement) (Bidonde 2014). Land-based exercise programmes showed a 9% absolute improvement in physical strength compared with the aquatic exercise. Overall these results are clinically insignificant.

Sleep hygiene

Sleep hygiene is a technique often used in CBT. Over 90% of people with fibromyalgia have problems with

BOX 2 Cognitive–behavioural therapy for chronic fatigue syndrome and fibromyalgia

Cognitive–behavioural therapy (CBT) is used widely in treatment of both chronic fatigue syndrome (CFS) and fibromyalgia. The basis for its use for these syndromes is that patients are thought to have a learned phobia of taking part in physical exercise for fear that they will develop exhaustion. CBT involves 'behavioural experiments' and graded exposure to activity. Graded exercise exposure is often delivered by a physiotherapist, on the principle that prolonged incapacity leads to deconditioning of muscles, after which symptoms arise from sudden exertion.

A Cochrane review of CBT in fibromyalgia reported 23 randomised trials with 2031 participants (Bernardy 2013). There was a modest improvement in pain scores, with a total mean pain score of 6.9 on a 10-point scale in the treatment arms, compared with 7.4 in the control groups at 6-month follow-up. This represents a small (4.2%) absolute improvement in pain scores (SMD = 0.29). There was also an 11.7% absolute improvement in disability scores (SMD = –0.30) at follow-up: those in the control group rated their disability at 2.8 on a 10-point scale, whereas those in the treatment group rated it at 2.0 (higher scores indicate greater disability).

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BOX 3 Key points on delivering graded exercise therapy

Graded exercise therapy (GET) is used widely in treatment of both chronic fatigue syndrome (CFS) and fibromyalgia. NICE advice on GET for people with CFS (National Institute for Health and Care Excellence 2007) can be summarised as follows:

- GET should be delivered only by a suitably trained GET therapist with experience in CFS, under appropriate clinical supervision
- Ideally, therapy should be one-to-one, with regular review of the programme and exercise diary (weekly if possible)
- Assess activity on referral and current activity levels
- Implement planned increases in the duration of aerobic physical activity (exercise that increases the pulse to 50–70% maximum heart rate) over months (exercise intensity should be measured using a heart rate monitor)
- Encourage exercise on at least 5 days out of 7
- Increase exercise by around 20% after the level has been sustained for 5–7 days and is tolerable – for example, start at 5 min exercise per day and increase to 6 min per day once this is tolerable for a week
- Aim to reach 30 min exercise per day – this needs to be maintained indefinitely
- Educate on sleep hygiene
- Teach and encourage practice of relaxation exercises
- Perform an activity analysis – to ensure that the patient is not cycling between excessive exercise and exhaustion
- Identify reasonable goals, such as twice-daily short walks to the shops, a return to a previous active hobby such as cycling or gardening or, for people with severe CFS, sitting up in bed to eat a meal
- Explain that the graded programme may initially produce a mild increase in symptoms such as stiffness and fatigue for a few days
- Advise that setbacks/relapses are to be expected – reduce activity to the previous level and split the period of daily activity into two sessions, attempt to identify any cause for the set-back such as an infection or disturbed sleep. After a set-back or relapse, slowly decrease the frequency and duration of rest periods.
- Try to maintain a regular but reduced programme of activity during set-backs
- Discourage daytime sleep
- Avoid advice to undertake unsupervised, unstructured or exhausting exercise (such as 'Go to the gym' or 'Exercise more'), as this may worsen symptoms

insomnia – a higher percentage even than in rheumatoid arthritis. Sleep hygiene involves prioritising restful sleep as a daily activity: ensuring that the bedroom environment is appropriate, with minimal noise and distractions; avoiding large meals, stimulants (e.g. coffee) and exercise prior to sleep; taking reasonable exercise during the daytime; hiding the clock; and using the bedroom only for sleep (Arnold 2012; Choy 2015).

A randomised trial compared 6 sessions of CBT adapted for insomnia with 6 sessions of conventional sleep hygiene in 64 women with fibromyalgia (Martínez 2014). At 6-month follow-up, 43% of the CBT group reported a clinically significant improvement in pain, compared with 31% of the sleep-hygiene group (12% absolute improvement; NNT = 8), although this was not statistically significant. There were similar improvements in measures of functioning.

Complementary medicine

Around 20% of patients with fibromyalgia will use acupuncture within 2 years of diagnosis.

Vas *et al* (2016) report a randomised controlled trial (RCT) of acupuncture for fibromyalgia involving 153 patients with a 10-week follow-up. Pain was assessed using a 100-point visual analogue scale. Pain intensity was reduced in both groups, but the reduction was greater in the acupuncture group (–41%; the mean baseline pain score was 77, reducing to 45) than in the sham acupuncture control group (–27%; baseline pain score was 79, reducing to 57). However, the mean pain scores at the end of the 10-week period remained high and were estimated at 45 and 57 on the 100-point scale in the acupuncture and sham-acupuncture groups respectively. At 12 months the benefits were statistically significant but much reduced (final mean pain scores estimated at 61 in the acupuncture group *v.* 74 in the sham-acupuncture group). Overall, there was a persistent medium effect size (0.5–0.6).

By contrast, a review of 9 RCTs of acupuncture involving 395 individuals with fibromyalgia produced a much smaller effect size (0.14); overall, at the end of treatment the acupuncture group rated their pain at 51 on a 100-point scale, compared with 70 in the sham-acupuncture control group; the NNT was ~4 (Deare 2013).

Hydrotherapy, homeopathy, chiropractic treatment and massage have also been widely used in fibromyalgia, although there are few rigorous trials. Nevertheless, these treatments are low risk and they are widely accessed by patients (Terry 2012).

Medication

A Cochrane review of antidepressants in fibromyalgia compared duloxetine and milnacipran with placebo over an average of 18 weeks in 10 randomised trials involving 6038 participants (Häuser 2013). This was supplemented by a later review of 18 trials of duloxetine in 6407 participants (Lunn 2014). All three drugs are serotonin and noradrenaline reuptake inhibitors (SNRIs). A clinically significant

improvement in pain (a 50% reduction in pain scores) was reported by 29% of the treatment group compared with 19% of the control group (NNT = 10; SMD = −0.23). There was minimal effect on disability. For duloxetine, the number needed to benefit was reported as ~8 at both 12 weeks and 28 weeks, on the basis of pain scores (Lunn 2014).

A Cochrane review of oxycodone for chronic neuropathic pain and fibromyalgia revealed 3 RCTs involving 254 patients in total (204 with diabetic neuropathy and 50 with post-herpetic neuralgia); no relevant trials were found for fibromyalgia (Gaskell 2014). These studies were of poor quality and often failed to report any intention-to-treat results or the proportion of patients showing a clinically significant reduction in pain score (conventionally, a reduction in pain score greater than 50%). The number needed to harm was 4.3 (1 more patient in every 4.3 reported a significant adverse reaction in the oxycodone group compared with the control group).

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (2014) reported that there was no convincing evidence to support the use of opioid ('narcotic') analgesics in fibromyalgia and advises against their use, although many patients with fibromyalgia continue to be prescribed these and the vast majority will have received long-term opioid analgesics at some point.

Neuropathic pain is thought to arise from damage to peripheral nerves or the central nervous system, rather than damaged tissues in the end organ. Neuropathic pain often fails to respond to conventional analgesics such as paracetamol and morphine (non-steroidal anti-inflammatory drugs and opioids). Cochrane reviews of placebo-controlled randomised trials of anti-epileptic drugs in neuropathic pain and fibromyalgia reported that only a minority of people received any clinically significant pain control using anti-convulsant drugs in any of the neuralgias (Wiffen 2012; Üçeyler 2013). Gabapentin and pregabalin were found to be effective in controlling pain from diabetic neuropathy and post-herpetic neuralgia (the NNT varied between 1 in 4 and 1 in 10), 'central neuropathic pain' (pain following a stroke) and fibromyalgia. An effect size of 0.28 was estimated for pregabalin in treatment of fibromyalgia (Üçeyler 2013). The anti-convulsant pregabalin is approved in the USA specifically for treatment of fibromyalgia. By contrast, there was evidence indicating that valproate, lamotrigine, oxcarbazepine and topiramate gave little or no effective pain control in fibromyalgia or other neuralgias. These reports defined a 'clinically significant' reduction as a halving in the mean pain scores on the various scales used in the trials.

Unfortunately, Cochrane reviews for neuropathic pain conditions report little evidence to support several other commonly used treatments, including amitriptyline, desipramine, nortriptyline, imipramine, carbamazepine and venlafaxine (Gallagher 2015; Moore 2015). An older double-blind RCT of a combination of tramadol and paracetamol in fibromyalgia involved 315 participants over 3 months. This study reported less pain at the end of treatment, although the effect size was small (pain scores of 53 *v.* 65 on the 100-point visual analogue scale; SMD = 0.28) (Bennett 2003).

Newer treatments for fibromyalgia include cannabinoids and low-dose naltrexone (Clauw 2014). Two small trials of cannabinoid (nabilone) treatment in fibromyalgia were reviewed by the Cochrane Collaboration (Walitt 2016). The trials were 4–6 weeks long and involved 72 participants. The benefits were unclear and the drop-out rate for the active treatment group was relatively high.

Chronic fatigue syndrome

Clinical features

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME) or neurasthenia, is a disorder of unknown aetiology characterised by unexplained debilitating fatigue and exhaustion continuing for more than 6 months which is not usually relieved by rest (Box 4) (National Institute for Health and Care Excellence 2007; Balachander 2014).

Research diagnostic criteria for chronic fatigue are often based on the Fukuda criteria, rather than less restrictive definitions such as the Oxford criteria. The Fukuda criteria require that chronic fatigue is accompanied for at least 6 months by unexplained short-term memory problems, sore throat, tender lymph nodes, muscle and joint pain and headache (Prins 2006). It usually begins at around 30–40 years of age.

There are several batteries of blood tests, as well as plain chest X-ray, recommended to exclude common causes of fatigue prior to a diagnosis of CFS. These include tests for anaemia, liver, thyroid, parathyroid and kidney disease, blood-borne virus infection, tuberculosis, rheumatoid arthritis, sarcoidosis and cancer, and more obscure immunological tests for chronic virus infections and Lyme disease (Afari 2003; National Institute for Health and Care Excellence 2007; Koch 2009). Whereas IBS and fibromyalgia are usually investigated by other specialists (gastro-enterologists and rheumatologists), individuals with CFS are often referred to liaison psychiatrists. Box 5 lists batteries of investigations that psychiatrists should consider for these patients.

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BOX 4 The Royal Free Hospital outbreak of encephalomyelitis

Chronic fatigue syndrome is perhaps the prototypical medically unexplained syndrome. Although the term was first used in 1988, there have been cases recorded for at least 200 years (Wessely 1994). George Miller Beard described neurasthenia, 'nervous exhaustion', in 1896. This came to be considered as a form of hysteria as psychoanalysis became fashionable in the early 20th century.

There was a famous 'outbreak' of a prolonged illness described at the time as encephalomyelitis in the Royal Free Hospital, London in summer 1955, where 292 staff members were taken ill over a 4-month period (although only 12 patients were affected). The initial symptoms involved fatigue and sore throat, progressing to pain in the neck, back and limbs, dizziness, blurred vision and muscle twitches. In retrospect, the initial symptoms are characteristic of a viral infection. Although no cause was ever identified for the outbreak, many of those affected were referred to psychiatrists and many were subsequently referred back by the psychiatrists as the disorder 'does not come into my field'.

Prevalence

The prevalence of fatigue symptoms in the community ranges from 5 to 20%, although the prevalence of strictly defined CFS is estimated at 0.2–2.6% (Prins 2006). The syndrome is around four times more common in women than in men.

Management

Treatment of chronic fatigue usually involves antidepressants, including SSRIs (e.g. sertraline) or venlafaxine to treat depression, or amitriptyline or duloxetine for both pain and depression. Antidepressants do not address the chronic fatigue itself (Pae 2009) and NICE states explicitly: 'No benefit was found in patients with CFS/ME from treatment with anticholinergic agents, antidepressants, anti-hypertensives or growth hormone' (Turnbull 2007). Many other agents have also been tried, such as stimulants (modafinil, methylphenidate and dexamphetamine), hormones (thyroxine, hydrocortisone and growth hormone) and immune modulators (acyclovir, interferons and amantadine), although these have seldom been found to be effective and are not recommended (National Institute for Health and Care Excellence 2007; Van Houdenhove 2010).

Psychotherapy is thought to be superior to medication in the treatment of CFS and usually takes the form of CBT with graded exercise exposure, relaxation training and sleep hygiene (Box 2 & Box 3) (Fulcher 1997; White 2011). Evidence is usually derived from trials involving patients with mild to moderate CFS rather than those with severe fatigue, who may be bedridden and therefore unable to attend hospital appointments.

The PACE trial involved six secondary care centres with 1-year follow-up of 641 participants who were randomised to receive one of four options: specialist medical care (SMC) alone, or with either adaptive pacing therapy, CBT, or graded exercise therapy (White 2011). Treatments were manualised and therapy sessions were audiotaped to ensure compliance with the manuals. Therapy continued typically every 2 weeks over 6 months, with the final follow-up at 6 months post-discharge. One of the active treatments in this rigorous trial was adaptive pacing therapy. The aim of adaptive pacing therapy was to encourage the participant to adapt to their illness by learning to identify triggers and situations that tended to exacerbate symptoms and then planning and pacing activity to reduce or avoid the associated fatigue. It is remarkable that adaptive pacing therapy remains very popular with patients, regardless of the results of the PACE trial (National Institute for Health and Care Excellence 2007). Overall, the PACE study initially reported that CBT and graded exercise therapy produced a significant but modest improvement in symptoms and physical activity (around 20% absolute improvement in scores). One re-analysis reported clinically significant recovery at 12 months in 3% of participants for placebo (treatment as usual), 6.8% for CBT, 4.4% for graded exercise therapy and 2% for patient-directed adaptive pacing (Racaniello 2016; Mitchell 2017). Regrettably, the PACE researchers subsequently reported that any benefit in the active treatment group appears to be lost at 30-month follow-up (Sharpe 2015).

A meta-analysis of 5 randomised trials of graded exercise therapy and 16 randomised trials of CBT produced a modest effect size of 0.28–0.33 (Castell 2011). The most recent Cochrane review of non-pharmacological treatment of CFS includes 8 trials with 1518 patients (Larun 2016). The review concluded that there was some benefit for active treatment in chronic fatigue, with 7 studies showing a significant difference in outcomes for fatigue symptoms at the end of treatment (typically a difference of 6 points between groups on the 11-point fatigue scale) (Larun 2016). There was no difference in many other symptoms, such as pain and overall health. However, the PACE study (White 2011) was the largest in the meta-analysis (641 participants), with a significant statistical influence on the overall analysis. Researchers and patient groups challenged the results of the PACE study soon after publication (Mitchell 2017). As

BOX 5 Suggested routine investigative tests and measurements in suspected chronic fatigue syndrome

- Chest X-ray
- Body mass index (weight and height)
- Blood pressure
- Urinalysis for protein, blood and glucose
- Full blood count
- Urea and electrolytes
- Liver function
- Thyroid function
- Erythrocyte sedimentation rate or plasma viscosity
- C-reactive protein
- Random blood glucose
- Serum creatinine
- Screening blood tests for gluten sensitivity
- Serum calcium
- Creatine kinase
- Assessment of serum ferritin levels (children and young people only)

Where the history is suggestive of an infection, immunological tests for:

- chronic bacterial infections such as borreliosis
- chronic viral infections such as HIV or hepatitis B or C
- acute viral infections such as infectious mononucleosis (use heterophile antibody tests)
- latent infections such as toxoplasmosis, Epstein–Barr virus or cytomegalovirus

More invasive or expensive investigations such as magnetic resonance imaging (MRI) of the head or endoscopy would be performed only if an appropriate specialist believed that the symptoms justified this

(National Institute for Health and Care Excellence 2007)

mentioned above, the favourable results for the PACE trial do not seem to be maintained at follow-up. This in turn is likely to influence the Cochrane meta-analysis.

There is limited research evidence to support diet and complementary therapies in CFS (National Institute for Health and Care Excellence 2007). Submissions to NICE by patient groups indicate that 60–65% of people with chronic fatigue found medication (especially hypnotics), diet changes and nutritional supplements helpful. Moreover, 89% found paced activity helpful (presumably the generic form of adaptive pacing therapy), and 91% found rest, including bed-rest, helpful. By contrast, 50% reported that graded exercise made symptoms worse; 26% found that CBT made symptoms worse and a further 67% found no benefit from CBT.

Conclusions

Patients with somatoform disorders are preoccupied with symptoms, the presence of an undiagnosed illness or other 'abnormal illness behaviour' (at least, in the opinion of many doctors). Indeed, one of the features of these disorders appears to be a conflict between the expectations of doctors and patients. The aetiology of medically unexplained syndromes has traditionally been presumed to be psychological – that is, a result of 'unconscious' processes, rather than physical disease. Nevertheless, medically unexplained syndromes such as CFS, fibromyalgia and IBS are notoriously disabling, persistent and difficult to treat.

Both CBT and graded exercise exposure require patients to increase activity, which often aggravates their symptoms, especially pain. Graded exercise therapy is often conducted by physiotherapists and commonly produces an increase in symptoms as the activity levels increase. This seems to make these options notably unpopular with patients, particularly compared with adaptive pacing therapy, which is self-directed.

There is some clear evidence from patient groups that many were unhappy with CBT and graded exercise therapy for chronic fatigue, reporting that they found it unhelpful – of course, this may be a consequence of patients being stigmatised as 'mentally ill' ('psychosomatic') when they are actually suffering from a physical disorder (National Institute for Health and Care Excellence 2007). Doctors, CBT therapists and physiotherapists may maintain that they would not regard medically unexplained syndromes as being 'psychogenic.' However, this does not seem to be the experience of patients. By contrast, complementary therapists (including those offering dietary advice and acupuncture) tend to validate the patient's sick role and complementary therapies are popular and widely used by patients (National Institute for Health and Care Excellence 2007).

It is likely that patients with fibromyalgia and IBS remain in contact with medical specialists (rheumatologists and gastro-enterologists), whereas patients with CFS are discharged by medical specialists after they have been referred to psychiatrists. Patients with chronic fatigue lack any further contact with 'conventional' organic medical specialists to validate the view that they have a physical disorder.

Selective diets and vitamin supplements are particularly popular with people who have chronic fatigue, especially in respect to symptoms of IBS, and alternative therapies (acupuncture and hypnotherapy) are often used for fibromyalgia symptoms, although these are not recommended by authorities such as NICE in the UK (National Institute for Health and Care Excellence 2007).

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There is a significant gulf between the beliefs and expectations of patients and medical professionals in the cause and treatment of medically unexplained syndromes, with patient groups rejecting the psychological aetiology of these disorders. This dispute is likely to have been aggravated by the longer-term follow-up of the PACE trial of psychological treatment for CFS, which validated patient groups and reported significantly poorer results than the initial analysis (Sharpe 2015).

When faced with patients who are disabled by overt physical symptoms, doctors are naturally challenged by their inability to find the cause of these symptoms despite ever more sophisticated investigations. These patients are often referred to liaison psychiatry, although the treatments available within mental healthcare (such as antidepressants and psychotherapy) remain of marginal benefit.

Regardless of their supposed causes, IBS, fibromyalgia and CFS remain common, extremely disabling and lack effective treatment. The suggestion that these syndromes may be 'psychogenic' is highly disputed by many patients and is likely to be a distraction from focused research into the potential neurological or physical cause.

MCQ answers
1 b 2 b 3 e 4 a 5 e

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MCQs

Select the single best option for each question stem.

1 Irritable bowel syndrome is commonly associated with:
- a Down syndrome and the syndrome of inappropriate antidiuretic hormone secretion
- b chronic fatigue and fibromyalgia
- c post-concussion syndrome and post-encephalitic syndrome
- d fibromyalgia and post-concussion syndrome
- e Down syndrome and chronic fatigue.

2 According to most definitions of 'chronic fatigue syndrome', unexplained debilitating fatigue and exhaustion should persist for at least:
- a 3 months
- b 6 months
- c 12 months
- d 24 months
- e 48 months.

3 Terms used in the classification of unexplained medical symptoms include:
- a somatoform disorder
- b functional disorder
- c psychogenic disorder
- d conversion disorder
- e all of the above.

4 The worldwide community prevalence rates of fatigue, fibromyalgia and irritable bowel syndrome among adults are estimated at:
- a 10–15%, 2–8% and 5–20% respectively
- b 30–40%, 50–60% and 40–50% respectively
- c less than 1% for each disorder
- d around 25% for each disorder
- e there are no reliable studies.

5 Widely used treatments for fibromyalgia include:
- a cognitive–behavioural therapy
- b sleep hygiene
- c acupuncture
- d antidepressants such as duloxetine
- e all of the above.