



British Association for CFS/ME: Therapy and Symptom Management in CFS/ME

Aim

This guide was developed through the British Association of CFS/ME (BACME), an organisation that represents health professionals working with this condition. It aims to provide information to support clinicians in their work with CFS/ME and includes both pharmacological and rehabilitative approaches. It has been developed by a group of experienced professionals both in a specially convened open workshop, held in 2014, and through circulation and consultation with the wider BACME membership, AYME (Action for Young people with ME) and service -users.

This document is compiled of two major sections. These two sections are:

1. Symptom management guide. This provides information about symptoms experienced by people with CFS/ME, and if pharmacological therapy can ease these symptoms. Information on contra-indications and cautions to consider is also provided for these pharmacological treatments.
2. Guidance for therapists covering the provision of therapy for CFS/ME. This includes a list of resources (available on the website BACME.info) for use in therapy, as well as guidance on support and supervision. It does not replace specialist CBT and GET training (recommended by NICE and available at www.PACEtrial.org). It represents pragmatic recommendations from experienced clinicians to guide practice when seeing adults with CFS/ME, where specialist CFS/ME CBT and GET therapists are not available/appropriate. It is informed by these approaches.

The term CFS/ME has been applied throughout this guide as it is the current term used in NHS services. Other terminology may be used by some clinicians, therapists and service users

A Brief History of CFS/ME services within NHS

In May 2003, it was announced that a central budget of £8.5 million would be released to the NHS in two phases to allow stepped development of CFS/ ME services in England. As part of this initiative 13 centers and 36 local teams for adult services and 11 specialist teams for children and young people were set up between 2004 and 2006 (http://www.bacme.info/document_uploads/POD_Docs/CFSMEServInvestProg0406.pdf).

These services now form part of the British Association for Chronic Fatigue Syndrome/ ME

(BACME), in partnership with patient charities and services that were already established prior to 2004.

History of BACME

The British Association for Chronic Fatigue Syndrome/ME (BACME) is a multidisciplinary organisation, which exists to promote and support the delivery of evidenced based treatment for children, young people and adults with CFS/ME throughout the UK. BACME is a voluntary organisation and is open to all UK-based health professionals and researchers involved in the diagnosis and/or treatment of CFS/ME using evidence-based practice.

BACME was formed in October 2009 following the merger of the CFS/ME Therapists Network and the Clinical Network Co-coordinating Centers National Collaborative. The aim of these networks was to encourage health professionals to share and develop clinical practice in the assessment and treatment of CFS/ME. BACME aims to support professionals from any discipline and across any area of health in the UK in improving care for people with this debilitating condition (www.bacme.info/).

Objectives:

- To champion evidence-based approaches to the treatment of CFS/ME, such as those recommended in the NICE guidelines
- To provide a forum for the monitoring and dissemination of new evidence for the management of CFS/ME as it emerges
- To advocate excellence in the provision of, and equity of access to, clinical services for children, young people and adults with CFS/ME
- To support the delivery of services and to enable services to maintain standards of care in the treatment of CFS/ME as set out in the NICE guidelines
- To use clinical expertise and evidence to influence and inform healthcare policy
- To promote, facilitate and provide training for clinicians and researchers from all disciplines involved in the diagnosis and treatment of CFS/ME
- To foster research collaborations and communication between clinicians, researchers, professional bodies and charities
- To facilitate patient involvement in the development of evidence-based services and to promote patient-centered care.
- To foster co-operation and collaboration with teams, charities and individuals that share these principles
- To encourage and facilitate the systematic and rigorous audit, benchmarking and evaluation of CFS/ME assessment, treatment and services.

Introduction to CFS/ME

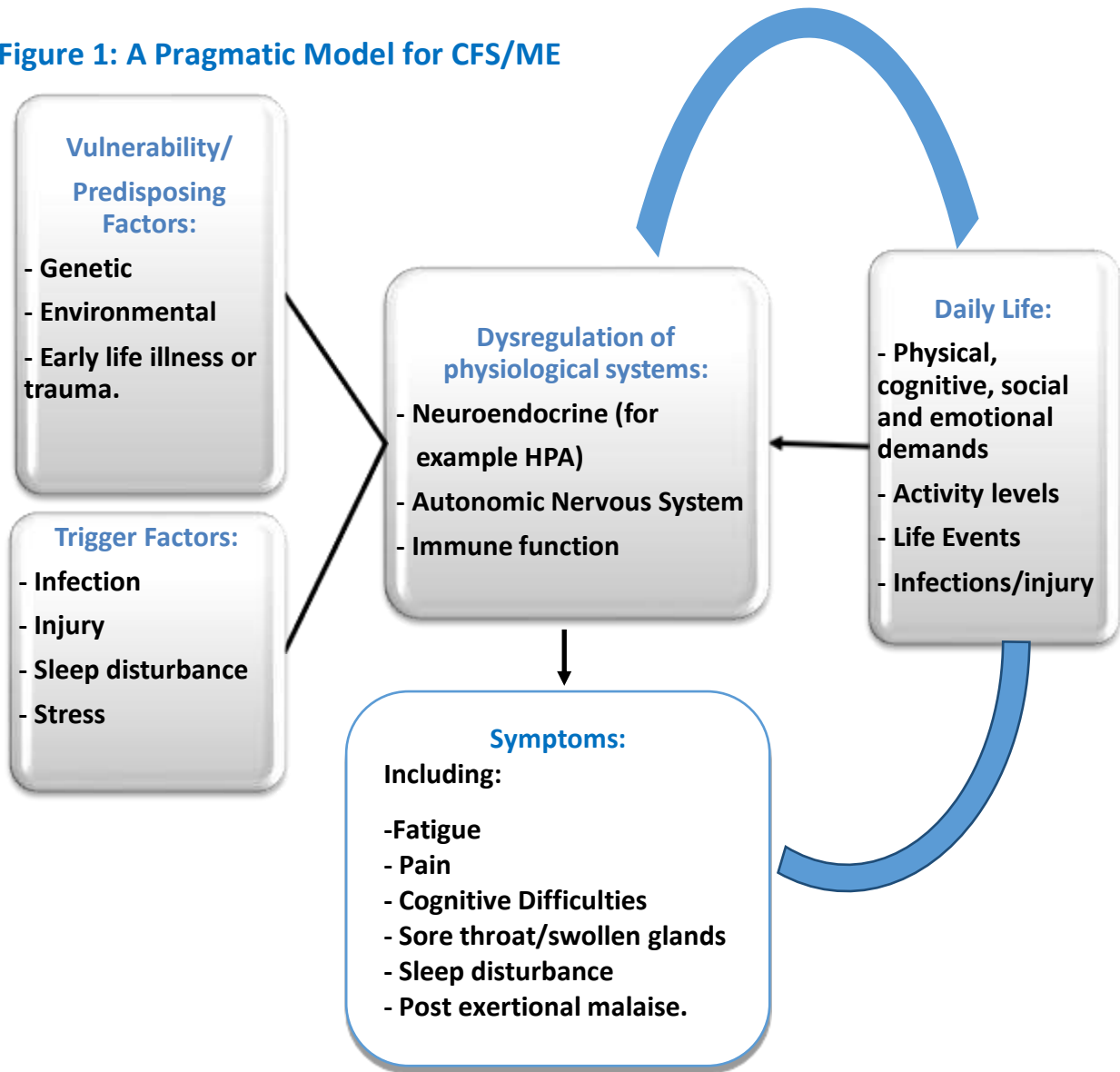
CFS/ME is a clinically defined syndrome with a characteristic pattern of symptoms but no consistent abnormalities on physical examination or on imaging/laboratory evaluation. It is often called a “diagnosis of exclusion” but in practice the symptomatology is frequently consistent enough to allow a confident positive clinical diagnosis to be made. The NICE guidelines recommend that a small number of investigations are carried out to exclude conditions that potentially could be confused with CFS/ME.

A Brief Synopsis of CFS/ME is provided at <http://www.bacme.info/aboutcfsme/>). It is very important that the person has a detailed medical examination by a doctor to exclude any other treatable condition. Continued monitoring of the patient is important in relation to any new symptoms, which may or may not be part of the illness profile.

Once a diagnosis has been made, patients should be considered for further evaluation to see if they would benefit from the evidence based treatments (CBT – cognitive behaviour therapy and GET – graded exercise therapy). Where these specialist services are not available, rehabilitation using those principles (as described later in this guide).

A pragmatic model of the condition is shown in Figure 1.

Figure 1: A Pragmatic Model for CFS/ME



Symptom management in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME)

Introduction

This guidance has been developed by a group of clinicians from the British Association for Chronic Fatigue Syndrome/ME (BACME). There is very little good clinical evidence in this disease area. It represents pragmatic good practice recommendations for GPs and other clinicians to guide prescribing practice when seeing adults with CFS/ME

As indicated above, CFS/ME is a characteristic set of symptoms with no consistently identifiable pathology. Asymptomatic CFS/ME by definition cannot exist. Therefore in addition to referral for definitive therapy (CBT and GET type interventions) patients with CFS/ME may need symptomatic remedies to help with specific symptoms whilst waiting for definitive therapy to become available and/or to become effective.

General Principles

- Treating clinicians should satisfy themselves that the particular symptom they are going to treat is attributable to CFS/ME and that no other condition requiring definitive treatment is likely to co-exist.
- Even when a diagnosis of CFS/ME has been well established, any new symptom needs careful evaluation to ensure that no additional pathology has developed.
- Each symptom should be identified, quantified and documented in order that the benefit from specific therapeutic interventions can be assessed.
- CFS/ME patients report being especially susceptible to adverse effects of drugs so if any non-pharmacological option exists it is sensible to try that first.
- When drugs for symptomatic relief are prescribed then it is sensible to start with small doses and increase the dosage slowly and steadily until either the symptom is controlled, the maximum recommended dose is reached or dose related side effects from the drug become intolerable.
- Once the symptom is controlled it may be appropriate to reduce the dosage again after a time and see if the symptom reappears. The general principle is to use the minimum effective dose for the minimum time that is necessary.
- If a drug is being ineffective then it should be withdrawn.
- It is better to use monotherapy to treat an individual symptom. If more than one drug has to be used then be aware of the potential for drug interactions.

There are four potential outcomes from introduction of symptomatic drug therapy:

- The symptom worsens or the patient suffers an adverse drug reaction in which case it should be withdrawn.
- There is no change in the symptom. In this case, the drug should also be withdrawn after an appropriate trial period that will depend on the particular symptom and drug.
- The symptom partially responds to the introduction of the drug in which case it should be continued and consideration given to attempting a dose increment bearing in mind the risks of adverse reaction. If no dose increment of this drug is feasible and the symptom persists then it may be reasonable to add a second drug.
- The symptom is completely relieved. Under these circumstances it makes sense to continue the drug for some time and then consider withdrawal as the patient's overall condition improves (perhaps in response to definitive therapy with GET or CBT).

Symptoms for which no Pharmacological Therapy is available:

Fatigue

Fatigue is clearly a cardinal feature of CFS/ME and it is chronic and disabling. It is not somnolence (sleepiness) and indeed, if somnolence is a predominant symptom then alternative/additional diagnoses (such as sleep apnoea) should be considered. There is no drug therapy that will improve fatigue – neither generally nor the specific fatigue of CFS/ME. However, improving sleep, mood or pain pharmacologically may indirectly improve fatigue.

“Payback”

A characteristic feature of CFS/ME is the way that many forms of over exertion (physical or mental) will lead to an exacerbation of fatigue and other symptoms. This phenomenon is often known colloquially as “payback”. Once again, no drug has been shown to mitigate this symptom.

“Brain fog”

This is another characteristic feature of CFS/ME and refers to the low grade confusion, memory loss and other cognitive difficulties experienced by patients with CFS/ME. There is no evidence that drug therapy will produce significant improvement in this.

Lymphadenopathy

CFS/ME patients will often complain of sore or tender lymph nodes usually confined to the cervical region. This may be intermittent and is often described as worsening in conjunction with other CFS/ME symptoms. This may give rise to anxiety on the part of clinician and/or patient that some alternative/additional condition is present such as a chronic infection or malignancy and clearly any new lymphadenopathy requires careful clinical (and potentially laboratory/imaging) evaluation. If it is decided that the symptoms are probably related to CFS/ME then there is no drug therapy that will improve them.

Recurrent upper respiratory infection

CFS/ME patients will frequently complain of recurrent sore throats or other features suggesting upper respiratory infection. These are often accompanied by the lymphadenopathy described above. Once again no drug therapy will have an impact on these symptoms and specifically, there is no role for prophylactic or frequent therapeutic antibiotics. Antibiotics should only be given where there is convincing evidence of an acute bacterial infection.

Symptoms that may potentially benefit from specific symptomatic treatments

There are a number of symptoms that occur with CFS/ME for which there are potentially symptomatic remedies and bearing in mind the general principles described above, it may be appropriate to try and ameliorate these.

Pain:

Pain associated with CFS/ME is comparable to the pain experienced in Fibromyalgia and persistent/neuropathic pain states so should be approached in a similar fashion.

CFS/ME pain is probably driven by central sensitisation of the central nervous system (CNS). Therefore, drugs that may help tend to be pain modifying drugs such as antidepressant and anticonvulsant drugs that have some efficacy in helping persistent pain.

Tricyclic antidepressant drugs (TCAs)

The best evidence for efficacy and tolerance is for low dose tricyclic medication. There are unlicensed but widely used for pain. They typically improve sleep quality and pain quicker than depression and benefit should be apparent within 1-2 weeks.

The most commonly used is amitriptyline at a starting dose of 10mg (or lower if needed using syrup - e.g. 1ml of 25mg/5ml oral solution). Typically start 2-4 hours before bedtime or 12 hours prior to desired waking up time. If tolerated but ineffective or partially effective, the dose can be titrated up to 75mg in the community.

If it is not tolerated due to excess sedation consider the alternatives:
Imipramine 10mg or nortriptyline 10mg are regarded as less sedating.

Cautions and contraindications:

These drugs should be used cautiously in patients with angle-closure glaucoma, benign prostatic hypertrophy, urinary retention, constipation, cardiovascular disease, or impaired liver function. They do have cardiotoxicity and generally should be avoided in patients with second- or third-degree heart block, arrhythmias, prolonged QT interval on the electrocardiogram, or severe liver disease and in patients who have had a recent acute myocardial infarction.

Side effects:

Excessive day time sedation/hangover and daytime cognitive impairment are common and may be helped by dose reduction, taking earlier in the day or switching to less sedating drug. Likewise dose reduction or switching may improve other side effects such as constipation, dry mouth, blurred vision, tachycardia, urinary hesitation) orthostatic hypotension and, weight gain.

Anticonvulsants

Certain anticonvulsant medications can be tried as an alternative to tricyclic drugs if they are being ineffective or can be added to tricyclics if they are being partially effective.

The most common two used are gabapentin and pregabalin. Although these can be effective, there is a potential for dependence and misuse and both patients and prescribers need to be aware of this. (Although generic pregabalin is available it is only licensed for epilepsy and generalised anxiety disorder.)

Gabapentin can be used in low doses in the evening e.g. 100-300mg to try and improve pain and sleep. If this does not help the dose can be escalated towards 600mg three times a day.

Pregabalin in gabapentin non-responders can be started at low dose e.g. 25mg three times a day and increased after 3-7 days to 50mg three times a day and then again to 75 or 100mg then 150mg three times a day (it can be simplified to twice daily dosing).

Cautions and contraindications:

Avoid abrupt withdrawal and cautious in elderly and those with diabetes mellitus

Side effects:

Neither are well tolerated with dizziness, somnolence, weight gain, peripheral oedema and negative neurocognitive effects often limiting tolerability.

Non-Steroidal Anti-Inflammatory drugs (NSAIDS)

These drugs e.g. Ibuprofen or naproxen may help if there is musculo-skeletal pain with stiffness such as in concomitant osteoarthritis. If they are used long term then consideration needs to be given to the risks of gastric irritation (and it may be necessary to co-prescribe a proton pump inhibitor or other form of gastric protection). There is also the risk of renal toxicity and therefore it is necessary to be cautious in diabetics or those with renal disease.

Moderate powerful opiates

These included codeine and tramadol based opiate-containing analgesics. They tend to be of limited efficacy in central sensitisation pain. Even if there is early benefit this may be lost within a few weeks and tolerance may develop. Short courses and avoiding maximum doses are probably best if they need to be prescribed. There is better evidence for tramadol than other analgesics in fibromyalgia and its use with full dose paracetamol at submaximal doses seems to limit tolerance.

Other potential drugs that may help as pain modifying drugs

Duloxetine is from another class of antidepressants that may help central pain and if there is associated depression then it may be the antidepressant of choice. It is widely used in fibromyalgia (see below).

Selective Serotonin Reuptake Inhibitors (SSRI).

There is inconsistent evidence on the use of Selective Serotonin Reuptake Inhibitors (SSRI). However they may be added on to low dose tricyclic drugs e.g. fluoxetine 20mg morning to improve pain and mood (hopefully without increasing sedation.) When used in

monotherapy they may need to be dose escalated to higher than typical doses to get benefit in pain e.g. fluoxetine 40-60mg.

Mirtazapine initially 15mg in the evening increasingly every 2 weeks to 30 then 45mg a day may be helpful especially if there is pain and concomitant significant depression and sleep disturbance

The best guidance to refer to is the NICE guidance on Neuropathic Pain although this guidance does not make reference to CFS/ME pain or Fibromyalgia where the pain mechanisms are probably different (<http://www.nice.org.uk/guidance/CG173>).

Gastrointestinal symptoms

Gastrointestinal (GI) symptoms are common in people with CFS/ME. As with all symptoms, their precise mechanism is ill understood but seems to resemble the autonomic dysfunction associated with other common conditions such as Postural Orthostatic Tachycardia Syndrome (POTS). There is a functional sensitivity in the gastrointestinal tract leading to upper GI symptoms such as nausea, indigestion, dyspepsia, acid reflux and lower GI symptoms such as pain or discomfort, bloating and change in bowel habit characteristic of Irritable Bowel Syndrome (IBS).

Although patients with CFS/ME frequently have GI symptoms they rarely ask for help with these and GP's are generally seem more comfortable dealing with them.

Nausea

Nausea associated with CNS causes such as migraine or vestibular disorders can be treated with antihistamines. There is no evidence any one antihistamine is more effective than another so duration of action and side-effects should determine choice.

Metoclopramide and domperidone both have recent safety warnings associated with them and should generally be avoided but may be considered if all else fails.

Functional Non-ulcer Dyspepsia

This covers symptoms of abdominal pain, fullness, early satiety, bloating and nausea. Small, frequent meals and low sugar diets can be helpful. . Antacids may be effective but most people need courses of a Proton Pump Inhibitor (PPI) such as:

Lansoprazole, omeprazole etc., or a histamine H2-receptor antagonist such as cimetidine, ranitidine etc.

All of the H2 receptor antagonists and omeprazole can be sold to the public over the counter (OTC) for a maximum of two weeks to alleviate symptoms i.e. obtained without a prescription.

Gastro-oesophageal reflux disease

This is associated with heartburn and acid regurgitation. Measures such as avoidance of smoking and alcohol, weight reduction and raising the head of the bed should be suggested.

Antacids can help mild symptoms and alginates such as Gaviscon or Peptac can form a 'raft' that floats on the surface of the stomach contents to reduce reflux and protect oesophageal mucosa. However most people need Proton Pump Inhibitors which are more effective than H2-receptor antagonists. (See above)

Irritable Bowel Syndrome (IBS)

The characteristic symptoms are those of abdominal pain or discomfort in association with an alteration of stool form or frequency. Other features include relief of pain or discomfort by defecation, abdominal bloating, and symptoms made worse by eating and passage of mucus. Nausea, backache and bladder symptoms are supportive of the diagnosis. The Rome criteria further subdivides patients into diarrhoea predominant (IBS-D), constipation predominant (IBS-C) or mixed (IBS-M).

- Antispasmodics such as mebeverine hydrochloride, alverine citrate, peppermint oil may reduce pain but antimuscarinics should generally be avoided particularly in IBS-C. Mebeverine can be sold to the public for IBS symptoms.
- Loperamide is the first choice of antimotility drugs for IBS-D.
- Osmotic laxatives such as Macrogol are preferred for IBS-C but Lactulose should be avoided as it can cause bloating.

Tricyclic Antidepressants (TCAs) such as amitriptyline, imipramine, nortriptyline starting with small doses (5-10mg equivalent of amitriptyline) can be used for the pain of IBS in a similar way to its use in the generalised pain of CFS/ME. There is no significant antidepressant effect at this dose and patients can often be encouraged to try it without the stigma of

psychotropic medication. TCAs may be more appropriate for patients with IBS-D, due to their constipating effects. Selective Serotonin Reuptake Inhibitors (SSRIs) such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline may be more suitable for patients with IBS-C or if TCAs are ineffective. Neither TCAs nor SSRIs are licensed for use in IBS.

Linaclotide, a guanylate cyclase-C receptor agonist, is licensed for use in the treatment of moderate to severe IBS-C. It should perhaps be used for patients who have not responded to other treatments. It is relatively expensive.

The use of fibre is controversial. Soluble fibres such as ispaghula husk, steckia or foods such as oats are probably helpful whereas insoluble fibre such as bran may exacerbate symptoms. Good fluid intake should be maintained.

There is emerging research to suggest that those with IBS symptoms may benefit from a diet in low fermentable carbohydrates. The Low FODMAP diet stands for fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. FODMAPs include wheat milk and a range of fruit and vegetables. Assessment should be by a dietitian as these diets are complex and restrictive and may be inappropriate for those with CFS. Any benefit of reduction in gut symptoms needs to be balanced with potential compromise in nutritional intake, and the extra effort and expense in following such a diet. The restriction of FODMAPs should be for 2 months and then followed by testing toleration of the food omitted systematically.

There are reports that a gluten free diet may benefit patients with IBS even who test negative for coeliac disease but there is no definitive trial evidence to support this.

Cognitive Behaviour Therapy (CBT), Hypnotherapy and psychological therapy are listed in the NICE guidance (61). They are probably of benefit in IBS but it is recommended they be reserved for patients who fail more conventional treatments.

Consideration should be given to dietetic referral for general advice that may help but also to assess impact this is having on nutritional intake as it can be severe with patients eating little to no food and so worsening all other symptoms.

Autonomic symptoms

Studies suggest that 89% of patients with a diagnosis of CFS/ME have autonomic symptoms. These can be quantified using a tool which is validated and clinically applicable called the

Orthostatic Grading Scale (OGS). This simple, clinically applicable, symptom assessment tool allows quantification of autonomic symptoms in relation to standing. Scores of 4 or above are considered to be consistent with orthostatic intolerance and scores of 9 and above consistent with orthostatic hypotension.

If patients presenting with CFS/ME describe postural dizziness then enquiring as to a recent or previous history of episodes of loss of consciousness is appropriate. Should they describe postural dizziness together with a history of a loss of consciousness, then the NICE syncope guidelines and the European task force guidelines should be consulted for further assessment, diagnosis and management of their syncopal symptoms. In the vast majority of instances this will involve formal autonomic testing, possibly including tilt table testing. The ideal scenario in these circumstances is to have this testing performed with continuous beat to beat heart rate and blood pressure measurement in order to allow subtle changes in blood pressure to be detected. The idea of a tilt table test is to reproduce symptoms in association with a change in heart rate or blood pressure. There is frequently a misconception that coming to the end of a tilt table test means that the diagnosis of neurally mediated hypotension is not applicable. This is not the case. It means that the amount of provocation that has been delivered during the tilt table test is not adequate to lead to changes in blood pressure and therefore the tilt table test needs to be repeated with appropriate provocation.

If an individual has postural dizziness and a diagnosis of positional tachycardia syndrome (POTs) is suspected then initially a standard two minute active stand may provide the diagnosis. This simply means measuring heart rate +/- blood pressure when lying, taking a mean value during rest at 10 minutes, and then asking the patient to stand as quickly as they can and seeing what happens to the heart rate and blood pressure over a short period of time. If this is not diagnostic but clinically the diagnosis is still suspected one should go on to perform a ten minute passive head up tilt. The diagnosis of POTs is made if the heart rate increases to above 120 on assuming the right position or by 30 beats per minute. These evaluations are best carried out in a specialist centre with expertise in this area.

Management

Neurally mediated hypotension is supported by a range of different management strategies. Individuals should increase their water intake to at least 2.5 litres of water a day, ideally with 1.5 litres before lunchtime. This is often very difficult for patients to accept. They can be advised that fluid is their “medicine”, and by taking a pint of fluid four times a day this will begin to refill the cardiovascular system. Patients are asked to reduce their caffeine to less than 5 cups a day, these are standard cups and patients should be reminded that tea

and coke can contain as much caffeine as coffee can. In certain instances, people who have low blood pressure should increase their salt intake and ensure that they do not take an excessive amount of alcohol. Conservative counter manoeuvres may be beneficial should they be symptomatic and there is a good body of evidence to support the use of leg crossing, arm clenching, etc. Tilt training and keeping a diary may also be helpful

Pharmaceutical Management of vasovagal syncope can be difficult. Having reinforced conservative advice and recommended to individuals to avoid situations that will bring on their symptoms there is the option to consider vascular expansion with medications such as fludrocortisone or to increase peripheral resistance with midodrine. However, try to avoid these medicines if at all possible.

POTs Management

With positional tachycardia syndrome all of the same conservative non-pharmacological advice should be followed. In recent years increasing evidence has arisen to suggest that many medications have side effects in patients with positional tachycardia syndrome that ultimately result in almost half of patients not being able to tolerate tablets. To date there are no randomised control trials of treatment in POTs, and medications if used are simply those that will provide symptomatic benefit. First line of treatment is a low dose betablocker.

Sleep disturbance

Sleep disturbance is common in patients with CFS/ME. Where getting to sleep/staying asleep is a problem and non-pharmacological strategies have not been sufficiently effective, medication can be tried in improving sleep. It is also worth clarifying whether there are additional factors impacting on sleep, such as pain, depression, anxiety, urinary frequency, sleep-wake cycle problems as addressing these factors may be important before night sedation is considered. Caffeine withdrawal is essential.

Amitriptyline at low doses (generally between 10 and 30mg) can be used which would benefit both pain and sleep and if present, migraines / headaches. There is wide variation between patients both in the dose that they will tolerate and the dose that produces any benefit. Those who are particularly sensitive may get significant side effects at 10mg, but sometimes tolerate and benefit from a lower dose administered using liquid preparation (25mg/5ml) which allows titration in 2.5mg to 5mg steps. Most patients take doses between 10 and 30mg, but morning sedation can be a problem and they may need to take the dose earlier in the evening. Alternative sedating TCAs may also be tried.

Other night sedation such as Zopiclone or Zolpidem could be used in the short term to try and regulate sleep patterns, but it would be advisable to keep it short term (up to 4 weeks) as tolerance can develop. Sedative antihistamines may also be useful. It is important that the medication is used in conjunction with other strategies to manage activity and sleep hygiene, as medication alone rarely has lasting benefit.

Melatonin is licensed to prescribe for over 55's for a maximum of 13 weeks at a dose of 2-4 mg nocte. If other contributing factors for poor sleep mentioned above is well controlled and yet sleep continues to be a problem, this may help regulate the circadian rhythm.

There is no evidence to support the use of stimulants in patients who have hypersomnolence. It is important that other causes of sleep disorders are excluded in these patients.

Mental health issues

CFS/ME is not a mental health issue. However, comorbid mental health problems should be treated as poorly controlled depression, anxiety disorders, obsessional compulsive disorder and post-traumatic stress disorder can significantly impact on the severity of CFS/ME. Psychological therapies should always be considered as the first option for these disorders, and there may be options of teletherapy for those patients who are unable to access outpatient treatment. However, for those patients with CFS/ME not in a position to pursue regular psychological treatments because of their fatigue and fluctuation of symptoms, pharmacological treatment of these disorders would need to be considered. This should follow the NICE guidelines (depression: <https://www.nice.org.uk/guidance/cg90>, Generalised anxiety disorder and panic disorder: <https://www.nice.org.uk/guidance/cg113>). The choice of medication will depend on the predominant symptoms.

Issues to take into account for patients with CFS/ME are:

As indicated in the introduction, it is sensible to start with small doses and build up the dose slowly. Both citalopram and fluoxetine are available in liquid form, so those who have difficulty with medication may start with a much lower dose than normally used: e.g. citalopram drops (40mg/ml) starting at one drop (2mg) building up every few days in one drop steps (4 drops is equivalent to 10mg tablet), or fluoxetine (20mg/5ml) starting at 4mg in 1ml, building up in 1ml steps. Sertraline can be started at 25mg (half the 50mg tablet) and built up to 100mg in the first instance. It is important to monitor their side effect and advise on rate of increase of dose soon after initiating the medication.

There is a potential risk of arrhythmias from QTc prolongation interval with citalopram/escitalopram that could be increased by co-administration of amitriptyline (that the patient may be taking for other indications such as pain and headaches / migraines.) If patients find the combination helpful it would be prudent to check their ECG for QTc interval if they need a combination of SSRI and tricyclic.

As many CFS/ME patients take analgesics, it is also worth bearing in mind that tramadol has serotonergic effects, and co-administration with SSRI's and SNRI's such as duloxetine have the potential to precipitate Serotonin Syndrome characterised by autonomic disturbance (hypertension, tachycardia, hyperthermia, sweating), neurological features (tremor, clonus, hyper-reflexia) and mental state changes (agitation, confusion, coma). It is important that the patients are warned to look out for these if tramadol and SSRI are prescribed and to report back to a doctor if reaction is suspected. Patients on a combination of non-steroidal anti-inflammatory drugs and SSRI's have an increased risk of gastrointestinal bleeding and should be on Proton Pump Inhibitors if they need to be on this combination.

Although mirtazapine (a noradrenaline and serotonin specific antidepressant) has the potential benefit of improving sleep and mood, there is a high risk of weight gain as a side effect, and as many CFS/ME patients put on significant amounts of weight after onset of their symptoms, this needs to be monitored if it is used.

Duloxetine is widely used in fibromyalgia patients in USA, and has recognised benefit for neuropathic pain though it is considered a second line drug for treatment of depression and generalised anxiety. Venlafaxine is in the same class of SNRI (serotonin nor-adrenalin reuptake inhibitor) and can be an effective second line antidepressant when SSRI's have proved inadequate. Blood pressure should be checked periodically if the daily venlafaxine dose exceeds 200mg a day.

Some patients experience withdrawal effects when stopping this medication and care needs to be taken when discontinuing. Some patients seem to benefit from this on both mood and pain, though it is considered a second line drug for treatment of depression and generalised anxiety.

Sedative antidepressants such as amitriptyline are rarely used at the antidepressant dose due to their potential to aggravate daytime fatigue.

'Allergic' symptoms

Rhinitis

True allergic disease forms part of the differential diagnosis of patients with fatigue. Chronic (perennial) rhinosinusitis, if severe, will cause generalised fatigue. However there will be evidence of nasal blockage and sinus tenderness. Diagnosis will be made by skin prick testing for inhalant allergens (or blood tests ('RAST' tests) for specific IgE antibodies), CT of sinuses may be appropriate.

Both fatigue and rhinitis are common problems and so may co-exist. A trial of high intensity anti-allergic therapy should be tried to see whether this improves fatigue. This should be with long-acting non-sedating anti-histamines such as fexofenandine or cetirizine. The dose may need to be increased above the doses stated in the BNF. Nasal symptoms should be addressed with nasal steroids (fluticasone) or a combination of nasal steroid with anti-histamines (fluticasone with azelastine). Correct head position is essential (head forward looking at the feet with the nozzle pointing away from the mid-line). It may be worth a trial of nasal steroid drops or oral corticosteroids if there is severe sinus disease on CT, as nasal steroid sprays may not penetrate adequately. Expect rapid resolution of symptoms on oral steroids, if they are due to allergy. Non-draining sinuses may require ENT intervention.

Environmental intolerance

Intolerance of environmental agents with strong smells (perfumes, cleaning products, smoke & fumes, solvents) may occur in CFS/ME (overlap with idiopathic environmental intolerance). Symptoms tend to be non-specific with malaise, headache, eye symptoms, and bowel and bladder symptoms. These are not IgE-mediated and allergy tests have no role. Avoidance is the mainstay. A useful questionnaire is the QEESI scoring system which can be downloaded from:

<http://drclaudiamiller.com/wp-content/uploads/2012/01/qeesi.pdf>

Drug therapy will rarely be tolerated and should be avoided.

Drug Allergy/Intolerance

Patients with CFS/ME frequently complain of multiple drug 'allergies'. The majority of symptoms will be non-specific intolerance or marked side effects, rather than true allergic reactions due to IgE or T cells. Psychoactive drugs are poorly tolerated and therapy should

start with the smallest possible dose, titrating up slowly. Liquid preparations are useful in this respect. Testing for true drug allergy is not usually required. Double-blind placebo controlled drug challenge can be useful in determining whether a drug can safely be administered.

Pharmacological approaches for which there is no evidence of benefit

None of these interventions are recommended but practitioners should be aware of them so that they can address patients' concerns and questions. If patients are taking dietary supplements and they are feeling benefit and if the intervention is not toxic or too expensive then it seems reasonable to acquiesce in their use but these interventions cannot be recommended nor made available on the NHS. Practitioners should note that there is no evidence that dietary supplements are effective.

Rituximab: Rituximab primarily destroys B cells and is therefore used to treat diseases which are characterized by excessive numbers of B cells, overactive B cells, or dysfunctional B cells, including auto-immune conditions.

A recent publication from Norway stated that in a study they had conducted there were beneficial effects of Rituximab on CFS/ME patients. If these effects are real and can be reproduced, the findings may guide us to understanding what causes CFS/ME.

Criticisms of the Norwegian study, some alluded to by the authors themselves, included the small number of patients participating in the study, and the high incidence of auto-immune illness already existing in the CFS/ME patients, or in their families. In addition, some of the tests and parameters used to measure the effects of treatment with Rituximab have not been used widely in previous trials, some of the methods used could have introduced bias, and statistical findings have been called into question. Finally, one of the major findings, the delayed response to reduction in fatigue by participants in this study, in comparison to the immediate response in all other auto-immune conditions in which depletion of B cells by Rituximab is used, has not been explained adequately.

A further open label study is being conducted in Norway, and funding is being sought to conduct an open label study in the UK. Some believe that the appropriate study would be a RCT and at present rituximab cannot be recommended.

Supplements and vitamins: In general, patients tend to be able to tolerate supplements better than prescribed medications, even though there is often equivalence in active ingredients. It is crucial to emphasize diet first, and to refer to www.food.gov.uk, an excellent website. Overall, it is useful to allow the patient to explore what might make them feel better. It will be at their own expense, possibly with the exception of vitamin D. So as to identify the relieving agent, the advice should be to introduce one supplement at a time.

Co-enzyme Q10: small studies have shown an improvement in cognition, and a more important study has shown a reduction in LDL. There are no identified DDIs. The patient can buy this OTC, and the advice about the dose would be to take the lowest dose tablet OD to start but it should not be recommended.

Vitamin C: Water soluble and therefore no risk of toxicity; dosage as in OTC multivitamin is perfectly adequate. For Linus Pauling aficionados, suggest 500mgs, but at their expense.

Omega 3. 6. 9: study outcomes are variable with respect to CFS/ME Toxicity is not an issue – emphasis is on diet first, but supplementation once a week can do no harm.

Magnesium: Information on the internet remains confusing; it is important to emphasise that Mg⁺ is filtered by the kidney, and we tend to retain, rather than excrete, what we need. Some with restless leg syndrome do find magnesium supplements beneficial, and advice should include low dosage and emphasis on side effects. Magnesium does have DDIs. Taking magnesium too close to a dose of some antibiotics, including quinolones, may interfere with absorption. Similarly, magnesium can interfere with absorption of bisphosphonates if taken together. Magnesium may increase the potency of metformin. Hypermagnesaemia is rare. Intravenous magnesium infusions are not recommended. Although a small study in the Lancet suggested benefit, those results have never been reproduced.

Vitamin D is a fat soluble vitamin so toxicity is possible with overdose. However, research indicates a multiplicity of important roles for Vitamin D, including bone and muscle integrity, cholesterol metabolism, deficiency increasing the rate of fibrosis in hepatitis C. The aim is to keep the level above 70.

Vitamin B12 IM and Folic Acid: There are some physicians who advocate and prescribe Vitamin B12 and folic acid for fatigue and fibromyalgia although again this has no evidence base.

Low dose naltrexone has no proven benefit and is not recommended.

Anti-infectives: Antibiotics should only be prescribed when there is good clinical or laboratory evidence of bacterial infection (e.g. a definite urinary tract infection or chest infection where there is a strong indication of bacterial as opposed to viral aetiology.) There is no role for long term antibiotics to treat putative causative agents such as Borrelia or mycoplasma etc. Nor is there any role for long term anti-fungal use.

Many patients will attribute the development of their CFS/ME to recurrent antibiotic use but there is no evidence for this.

Conclusion

Currently there is no pharmacologic agent that has any influence on the natural history or prognosis of CFS/ME and all patients should be considered for referral to specialist services for rehabilitation and support. Some CFS/ME symptoms are amenable to drug therapy, however and it is hoped that this guide will help with their appropriate use.

CFS/ME Guidance for Therapists

(To be used in conjunction with the resources available at BACME.info)

Purpose

This approach emphasises a person-centered collaborative that can be delivered in an interdisciplinary way. It is specifically focused on the therapeutic rehabilitation pathway and does not cover diagnostic issues. These foundations can be built upon by individual clinicians with profession specific skills and interventions.

The manual aims to reference both research evidence and clinical expertise but is primarily about the pragmatic implementation of these ideas in practice.

We hope that therapists may find this helpful to appraise and refresh their practice and access new resources, whatever their background and training.

Approach

The therapy should be built around the relationship with the person with CFS/ME. Therefore, this should not be seen as a one size fits all model, but an on-going, non-judgmental conversation and dialogue. Therapy is a collaborative process of both the therapist and person with CFS/ME sharing knowledge, agreeing realistic goals and reflecting upon experience. It is recognised that each therapist using this manual will also have an individual and professional perspective which can enhance the core approach described.

There is a large range of complementary resources, contributed by CFS/ME therapists, available from the BACME website.

Overview of the therapy

This section has two parts, within which there are numerous subsections to cover each area. The guide is written with each part of the therapy process in a different colour.

As the remit of the guide is active therapy it does not cover diagnosis and causation. It is a pragmatic framework for understanding the condition and therefore the rationale for the rehabilitation approach is included. This also forms part of the dialogue with the person with CFS/ME in forming a therapeutic alliance. Guidance on managing co-morbidities, identifying red flags and dealing with symptoms that cannot be addressed within therapy is outside the remit of this document.

Part 1 – Phases of Therapy

In the next section the guide focuses on phases of therapy as people will have different requirements at different stages of their condition. This is not intended to be a fixed process but reflect the development of therapy in relation to the individual's needs. Evidence based therapies emphasize a therapeutic relationship that enables a graded increase in activity and a process to explore barriers to this increase. From this evidence we felt there were 4 phases to successful CFS/ME therapy. Active verbs have been suggested to describe these phases:

- Engaging
- Regulating
- Increasing
- Sustaining

There is an expectation that there is a continual assessment and review process throughout each phase. There is no presumption of timescale for each phase, as each individual will differ. Some will need to consolidate strategies at each phase and may not require direct contact with a therapist during this time. This is not a linear process; for example, a person may have a relapse and find it beneficial to focus again on regulating. It is useful for both therapist and patient to understand that this is a dynamic process, not a procedure.

Part 2 – Delivering Therapy

In this section broader issues related to the delivery and adaptation of therapy are discussed. This includes delivery modalities, team working and dealing with difficulties that may occur within the therapy process. On-going supervision is an essential component of delivering therapy from an individual and team perspective.

Part 1 – Phases of Therapy

This part of the guide will give a detailed view of the components of therapy. It progresses from working with people to engage them in the approach to establishing their needs, reducing fluctuation and supporting improvement.

Therapy is designed to work with all the above processes described in the pragmatic model. The aim of a rehabilitation plan is to regulate bodily systems and to begin to desensitise a heightened level of sensory processing inside the body by doing a small amount (a baseline) of activity and achieving a better balance of rest in all areas of activity in daily life. Having achieved this, the challenge is to then gently build up activity over time thereby re-educating the body and increasing tolerance for exertion.

The figure below is designed to show the relationship of the phases and potential journey through therapy for the person with CFS/ME. Individuals will need to be assessed as to the phase they are in. The person may already be within a particular phase, such as they may have regulated and are ready to increase. People may transition through stages at different rates and have different needs depending on the severity of their condition.

Aims of each phase of therapy:

Engaging:

To engage the patient in a relationship (with the therapist) that facilitates collaborative working to achieve the person's goals with help of therapist's expertise and knowledge base through self-management and making changes.

Regulating:

To reduce the variation (boom and crash pattern) through stabilising daily routines, including physiological cycles such as sleep, eating and moving. This provides a sense of control and enables the person to have a foundation for improvement. For some people this may help achieve their goals or for some the goal may be to achieve regulation and stay at this level.

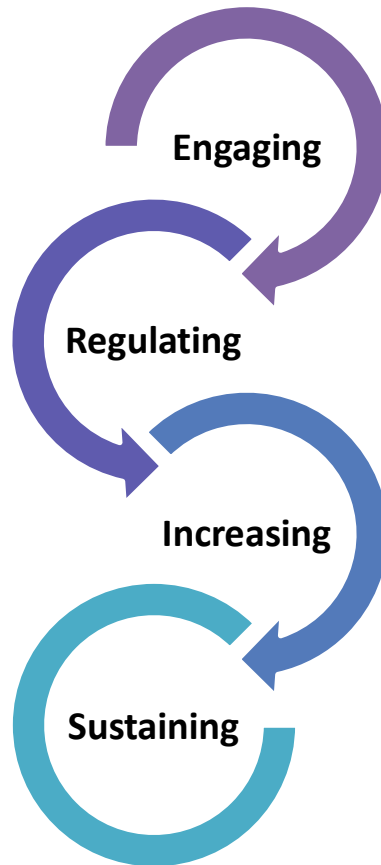
Increasing:

To gradually build the level of all areas of activity in daily life, as defined by the person. This may be increases in frequency, intensity, quality and/or duration. This is a consolidating, incremental approach that supports successful integration and can be sustained.

Sustaining:

To continue improvement towards recovery whilst accommodating the demands of daily life over time.

Figure 2: The Phases of CFS/ME Therapy



The table on the next page outlines the phases of therapy, the relationship to the therapy thematic content and the possible (not exhaustive) tools and resources for each phase. It is important that each person is assessed and the program is individually tailored. Therapists should select tools that are within their own professional competencies and therapeutic style. It is not intended that every option is given to every patient. Throughout the therapy journey barriers to change or progress need to be addressed; these will also be discussed more fully in Part 2.

Table 1: CFS/ ME Therapy Phases, Themes, Tools & Resources Summary

Phase	Therapy Themes	Illustrative Tools & Resources
<p>Engaging</p>	<p>Subsections:</p> <ul style="list-style-type: none"> ▶ Assessment for therapy and agreeing a formulation, should include <ul style="list-style-type: none"> ■ Information on background and onset ■ Symptoms (historical and current/other conditions). ■ Impact on routines, habits, patterns and lifestyle. ■ Physiological wellbeing (diet, sleep, relaxation, exercise) ■ Cognitive function (memory, concentration, attention) ■ Emotional wellbeing (mood, anxiety) ■ Social Environment (family, friends, finance, work, study) ■ Current self-management strategies (what makes it worse or improves it) ■ Hopes and beliefs related to condition (what the patient thinks is wrong) and therapy. ▶ Establishing a therapeutic alliance. Therapeutic strategies that enable the above include : <ul style="list-style-type: none"> ■ Listening, actively hearing the story ■ Validating; ; empathising and demonstrating belief ■ Communication; verbal & non-verbal, using their words. ■ Shared understanding of the individual's experience. ■ Developing a common understanding and formulation around their illness. ■ Explaining the rationale for therapy and information on the model ■ Collaboration and co-creation of their individual plan. ■ Agreeing their readiness for change & 	<ul style="list-style-type: none"> • Conversation • • Assessment framework, standardised assessment forms. • Standardised assessment & outcome measures – minimum data set (MDS) • Team model of illness & therapy, metaphors, diagrams and text information. • Model of change • Mutually agreed plan to progress • Copies of letters/summary outlining the assessment • Professional individual, peer and team supervision. • Contact with/narratives from other people who have participated in rehabilitation, e.g. through groups, DVDs, podcast, volunteers. <div data-bbox="1018 1339 1388 1899" style="background-color: #4a4a9a; color: white; padding: 10px; margin-top: 20px;"> <p>Collaborative goals and action plans: Set priorities & targets that are realistic with achievable steps towards the goal. In this stage this would mean overall goals for therapy.</p> </div>

approach, is this the right time and allowing people to opt in/out.

- Consideration and identification of the barriers they experience.
- ▶ Engaging in the model and their pathway to recovery.
 - Providing information on the therapy model.
 - Exploring how this model will benefit the individual.
 - Agreeing the model for delivery of therapy that best meets their needs.

Phase	Therapy Themes	Illustrative Tools & Resources
Regulating	<p>Subsections:</p> <ul style="list-style-type: none"> ▶ Patterns to support physiological homeostasis. <ul style="list-style-type: none"> ■ Sleep/ diurnal rhythms. ■ Nutrition ■ Activity – consistency and tempo. ■ Movement, exercise & posture ▶ Balance of daily life, reducing variation. <ul style="list-style-type: none"> ■ Duty versus pleasure/ fun, ■ Work, study, home and social life ■ Establishing patterns of planned activity and rest. ▶ Quality sleep, rest & activity <ul style="list-style-type: none"> ■ Enhancing parasympathetic activation – relaxation, sensory approaches, mindfulness ■ Exploring understanding about sleep, activity and rest. ■ Doing differently and reducing impact. ▶ Beliefs, sense of control & self-efficacy <ul style="list-style-type: none"> ■ Exploring beliefs around self, illness and exertion. Understanding acute v chronic models of health. ■ Expectations, priorities & choices ■ Addressing factors that increase low mood or anxiety. ■ Increasing self-compassion with permission to stop or change. ■ How to communicate and be assertive about own needs. ▶ Dealing with physical and social environments & relationships, including liaising with other services, such as care agencies. ▶ Establishing a starting point (baseline) as a basis for increasing. ▶ Dealing with Barriers, what are de-stabilising factors? Collaborative problem 	<ul style="list-style-type: none"> • Education and information • Diaries; sleep, daily activity, diet, thoughts (regular planning &/or recording) • Specific measures and outcomes, e.g. sleep, balance, posture, mood, activity. • Posture & Movement information; fitness triangle (strength, stamina, suppleness) pedometers/ actimeters, mobile apps, equipment to optimise ability • Relaxation training; CDs, websites, apps, podcasts. • Sensory interventions. • Metaphors • Case examples • Illustrative diagrams • Reflective enquiry • Support from other people/agencies to meet daily needs. <div data-bbox="1023 1294 1394 1899" style="background-color: #4b0082; color: white; padding: 10px; margin-top: 20px;"> <p>Collaborative goals and action plans: Establish plans to stabilise variable patterns in daily life – e.g. setting goals for sleep, rest, activity, socialising, diet, etc. that can be implemented consistently.</p> </div>

Phase	Therapy Themes	Illustrative Tools & Resources
Increasing	<p>Subsections</p> <ul style="list-style-type: none"> ▶ Reviewing and refreshing the starting point (baseline) ▶ Intention and desired destination <ul style="list-style-type: none"> ■ Dealing with expectations / standards and priorities ■ Setting realistic goals in line with core values ▶ Collaborative grading, <ul style="list-style-type: none"> ■ Analysis (all components of activity; physical, mental, emotional, cognitive, social) ■ Re-introduction of activity and/or exercise. ■ Agreed phased, incremental increases to physical, cognitive and/or social activities. ▶ Doing differently <ul style="list-style-type: none"> ■ Real world analysis (contextualising); environment, social, physical, work, study, home life, exercise. ■ Setting up Experiments that enable positive risk taking, with support needed and rewards. ■ Reflective Review – looking at shared understanding, awareness, meaning, progress, and barriers. ■ Recognising change/achievements ■ Making sense of arising symptoms & experiences (normalising) ■ Modifying (talking through, closing loops) ■ Solution finding ■ Communicating changes to others/assertion. ▶ Dealing with variation, priorities & choices 	<ul style="list-style-type: none"> • Diaries; sleep, daily activity, diet, thoughts • Experiments • Monitoring or recording for experiments. • Problem solving • Managing obstacles • Experiential learning in and out of sessions. • Metaphors & case examples • Verbal and written goal sheets can include confidence and importance scales. • SMART goals • Priorities review • Setback management • Reflection on changes and progress towards goals <div data-bbox="1018 1227 1390 1834" style="background-color: #4b0082; color: white; padding: 10px; margin-top: 20px;"> <p>Collaborative goals and action plans: Setting specific, measureable action plans or incremental goals that increase frequency, intensity, quality or duration of defined activities that is sustainable</p> </div>

	<ul style="list-style-type: none"> ▶ Consolidation, ensuring an increase can be sustained before moving forward. ▶ Dealing with Barriers, discussing what represents progress or is inhibiting it and exploring solutions. 	
Phase	Therapy Themes	Illustrative Tools & Resources
Sustaining	<p>Subsections</p> <ul style="list-style-type: none"> ▶ Preparing for end of therapy <ul style="list-style-type: none"> ■ Recognising resources; internal, external ■ Relapse planning ▶ Self-management of grading <ul style="list-style-type: none"> ■ Sense of mastery/ balance ■ Re-integration into life settings. ▶ Planning the future <ul style="list-style-type: none"> ■ Keeping it going; work, study, home life, social ■ Problems solving barriers ■ Reviewing conceptualisation of being well/normal energy. 	<ul style="list-style-type: none"> • Networks • Relapse plans <div style="background-color: #5d4037; color: white; padding: 10px; margin-top: 20px;"> <p>Collaborative goals and action plans: Setting longer term goals for maintaining well-being that reduce the risk of relapse and sustain long term improvement.</p> </div>

Part 2 – Delivering Therapy

1. Modes of delivery

Therapy can be delivered through individual or group formats; many people benefit from a combination of both.

- ▶ **Individual** – examples of different models of delivery - face to face, telephone, email, tele media and home based (primarily for those severely affected).
- ▶ **Group** – examples of different models of delivery - one-off sessions or timed, specific closed group programmes, for example 4 – 10 sessions. Groups can be educational or based on a specific therapeutic model. The number of group members may make a difference to therapeutic benefit.

There needs to be a rationale for the choice, mode and technology used for each person which meets their needs. Factors that may influence the choice of mode:

- Accessibility and transport
- Level of current activity and phase of therapy.
- Power of common experience through groups.
- Tolerance for engaging in therapy.
- A tool to increasing activity, e.g. through increased socialisation/regular attendance.
- Ability to engage in a group process.
- Available time or fit with current daily schedule.
- Content/purpose of sessions.

If using tele media the evidence suggests that least 2 individual sessions have most benefit before remote contact.

2. CFS team

This guide can be delivered by any health care professional with a specialist interest, training and supervision in CFS/ME. As the scope of the guide is wide, then each professional needs to be aware of their own service specification as well as their own skills and style.

An interdisciplinary approach is often favored by patients as they don't have to meet with as many health professionals. We felt that it was helpful to distinguish Interdisciplinary working from generic work, each member aware of core skills from own profession and additional skills from CFS/ME therapy

training and experience. Members of team can include: physiotherapist; psychologist; occupational therapist; medic; nurse; dietician; counsellor.

3. Supervision and support

In the development of the guide it was felt that training professionals in the delivery of CFS/ME therapy was only a beginning. In order to embed good practice and a flexible needs led service, then supervision from another CFS/ME therapist would be essential to maximize learning for the therapist and the service user. We suggest the establishment of a network of supervisors from different professions who are experienced in CFS/ME and utilise the approaches outlined in the NICE guidelines (CBT and GET) and this guide for individual and team supervision either in person or via Skype. Peer supervision within teams can also help embed good practice and deepen understanding, particularly when different presentations of CFS/ME need different approaches.

Other supervision considerations could include:

- A different profession to supervise could be useful to develop skills and understanding.
- Shadowing other therapists could be a key to training.
- Keeping up to date with developments in the field (such as BACME).
- Local peer groups; national networks- yahoo group, email etc.
- Lone workers or very small teams would need to consider how to manage complexity of cases and may want to consider having informal networks for supportive supervision either from colleagues or therapists in other teams.
- Due to the complex nature of the condition, therapist self-care and care of team members needs to be addressed by all members of the team. Small teams and lone workers may find networking with other adjacent teams useful.

3. Employment and education issues

Employment issues can be complex but are an important aspect of rehabilitation that can be addressed throughout therapy. Awareness of appropriate legislation and sources of support locally will increase the effectiveness of work in this area. Therapists would need to be aware of the scope of their service and may find the most effective thing to do is sign post to organizations such as Citizens Advice Bureau, Unions and Access to work. CFS/ME

therapists can be help by focusing on baselines of activity and applying the same principles of stabilizing and then gradually increasing work. Advocating for longer phased returns could be of required.

Action for ME has useful resources see:

<http://www.actionforme.org.uk/get-informed/employment>

For education see AYME

<http://www.ayme.org.uk/parents-and-schools>

Examples of interventions could include:

- Primary focus- implementing changes that the individual can make themselves at home and work. Maintenance of relationship with manager. Small adjustments in workplace- short rests, managing home life so work is easier. Health and safety legislation re IT usage which recommends breaks and task switching- see <http://www.healthyworkinglives.com/advice/work-equipment/display-screen-equipment-dse#legislation>

- More complex intervention possibly in liaison with Occupational Health and possibly unions: Equality Act (2010) <https://www.gov.uk/equality-act-2010-guidance> which includes: disclosure; Reasonable adjustments (E.g. reduced hours, breaks, sick leave management, and position of desk. Access to work can help with transport, practical support in the work place such as equipment etc. (<https://www.gov.uk/access-to-work>)