British Association of Clinicians in ME/CFS

ME/CFS
Guide to Symptom Management

2022

Document History

Year	Format/changes
2014	Original Document – incorporated with the Therapy Guide
2020	Original Document split into 2 separate documents: Guide to Symptom Management and Guide to Therapy Introductory section rewritten, CFS/ME changed to ME/CFS, index introduced, minor amendments to supplement section, weblinks updated.
2022	Reviewed following publication of 2021 NICE Guideline. Addition of section on Menstrual related Symptoms. This is a living guide which will be updated in response to developments in research and clinical practice.

Aim

This guide was developed through the British Association of Clinicians in ME/CFS (BACME), an organisation that represents health professionals working with people who live with ME/CFS. It aims to provide information to support clinicians in their work with people with ME/CFS. It was 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 (Association for Young people with ME) and service - users. It has since been briefly reviewed according to the new NICE guidelines (2021).

Originally one guide was produced to include both pharmacological and rehabilitative approaches. In October 2020, the single guide was divided into two to improve accessibility. These two sections are:

1. Guidance for therapists covering the provision of therapy for people with ME/CFS. This includes resources for use in therapy, as well as guidance on support and supervision. It represents pragmatic recommendations from experienced clinicians to guide practice when seeing adults with ME/CFS and is informed by clinical and research evidence. It does not replace specialist training in understanding and working with people with ME/CFS.

2. Symptom management guide. This provides information about symptoms experienced by people with ME/CFS, and if pharmacological therapy can ease these symptoms. Information on contra-indications and cautions to consider is also provided for these pharmacological treatments.

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

Introduction to ME/CFS

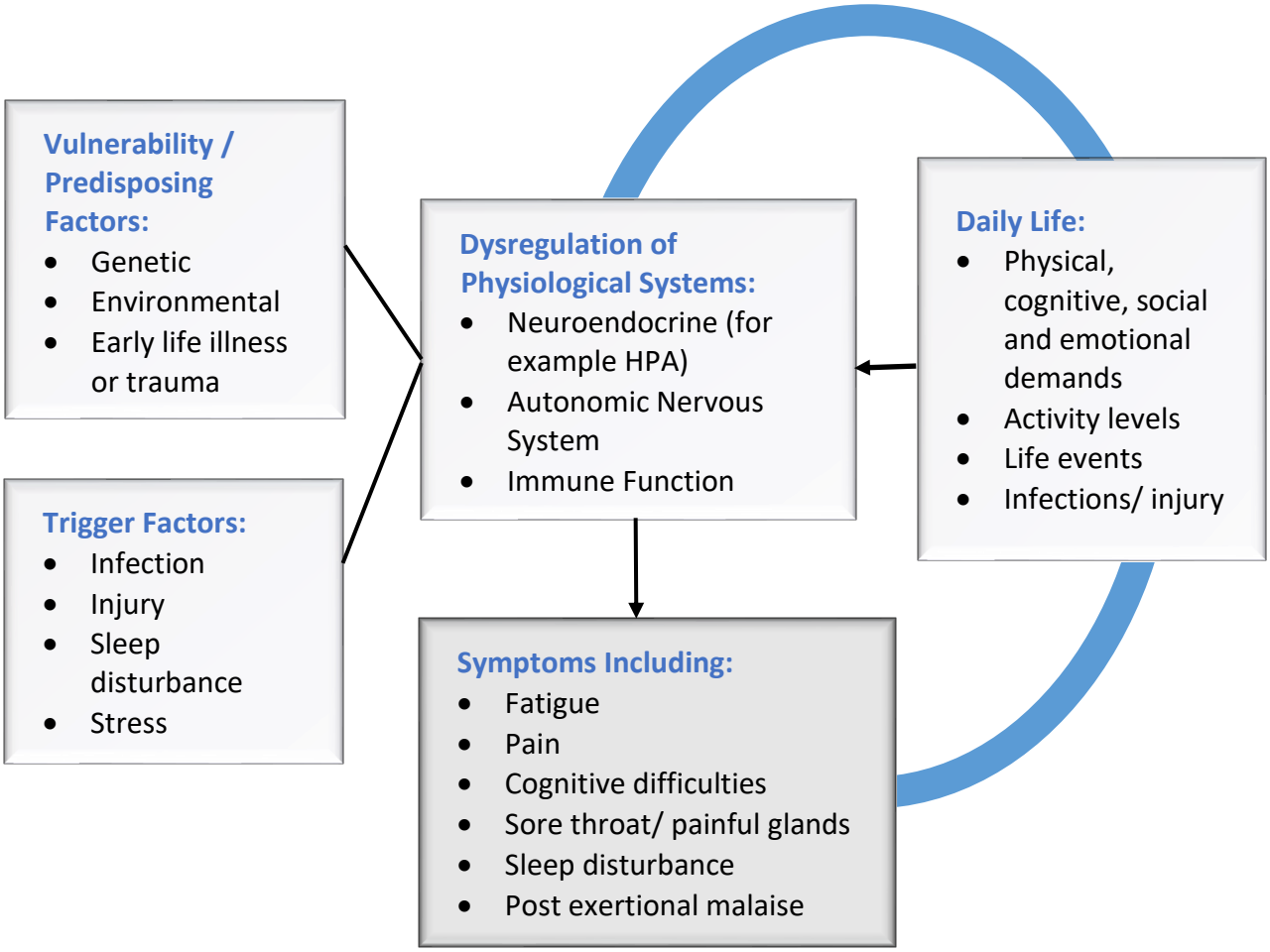
ME/CFS is a serious, complex, chronic multi system illness that can profoundly affect the lives of people who develop it. There is evolving evidence to indicate a dysregulation of multiple dynamic physiological systems in explaining the symptom picture seen in ME/CFS involving demonstrated changes in Immune System responses, Autonomic Nervous System function, Neuroendocrine pathways including the Hypothalamus-Pituitary-Adrenal axis along with cellular metabolic changes. ME/CFS 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. It is very important that the person has a detailed medical examination by a doctor to exclude any other treatable condition. The NICE guideline recommends that a number of investigations are carried out to exclude conditions that potentially could be confused with ME/CFS.

Continued monitoring of the patient is important in relation to any new symptoms, which may or may not be part of the illness profile.

NICE guidelines recommend that a diagnosis should be made if symptoms persist and are unexplained by another condition for 3 months. They should then be referred to a specialist ME/CFS team.

A pragmatic model of the condition is shown in Figure 1. A more detailed explanation of this model which involves multi-system dysregulation is available from the BACME website.

Figure 1: A Pragmatic Model for ME/CFS



Introduction to The Guide to Symptom Management

This guidance has been developed by a group of clinicians from the British Association of Clinicians in ME/CFS (BACME). There is very little good clinical evidence in this disease area. Symptoms can be managed but there is currently no cure for ME/CFS. Much of the mainstay of treatment is to employ principles of energy management with pacing, planning periods of restorative rest and activity, sleep hygiene and to educate people to be aware of their personal energy limits and to try to avoid 'booming and busting'. There are no medications specifically licensed for use in ME/CFS. This guide represents pragmatic good practice recommendations for GPs and other clinicians to guide prescribing practice when seeing adults with ME/CFS.

General Principles

- Treating clinicians should satisfy themselves that the particular symptom they are going to treat is attributable to ME/CFS and that no other condition requiring definitive treatment is likely to co-exist.
- Even when a diagnosis of ME/CFS 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.
- Offer patients a medication review in line with NICE guidance on medication adherence and medicines optimisation.
- Drug treatment for children with ME/CFS should only be initiated under supervision from a medical professional trained in paediatric prescribing.
- ME/CFS patients report being especially susceptible to adverse effects of medications and can experience exaggerated responses 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 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 the consider withdrawal as the patient's overall condition improves.

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Symptoms for which no Pharmacological Therapy is available

Fatigue

Fatigue is clearly a cardinal feature of ME/CFS 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 ME/CFS. However, improving sleep, mood or pain pharmacologically may indirectly improve fatigue.

Post Exertional Malaise

A characteristic feature of ME/CFS is the way that many forms of over exertion (physical or mental) will lead to an exacerbation of fatigue and other symptoms. The escalation in fatigue can occurring during or immediately after doing an activity but the typical Post-Exertional Malaise pattern is where there is a delayed further escalation in fatigue and other symptoms which can happen hours or days after the increase in activity. After a flare-up, it will often take patients a long time to recover to their previous levels. This will vary from patient to patient. Once again, no drug has been shown to mitigate this symptom.

Brain fog

This is another characteristic feature of ME/CFS and refers to the low grade confusion, memory loss and other cognitive difficulties experienced by patients with ME/CFS. There is no evidence at this stage that drug therapy will produce significant improvement in this. Medications such as Modafinil or other stimulants do not have established efficacy or safety data and are therefore not recommended.

Lymphadenopathy

ME/CFS 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 ME/CFS 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 ME/CFS then there is no drug therapy that will improve them.

Recurrent upper respiratory infection

ME/CFS 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 ME/CFS 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 ME/CFS is comparable to the pain experienced in Fibromyalgia and persistent/neuropathic pain states so should be approached in a similar fashion. Non-pharmacological methods for managing pain are more likely to help and should always be considered first and continued alongside any medications used for pain management.

ME/CFS 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. There are increased risks associated with using them alongside other antidepressant medications such as SSRI's.

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.

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 musculoskeletal 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. Long term use has also been associated with vascular and cardiac risks.

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. Long-term regular use of opiate medications are now known to often aggravate chronic pain conditions and cause increased hyperalgesia. They can also cause sleep disordered breathing and disrupt normal hormone systems and therefore can

have negative impacts on fatigue and other ME/CFS symptoms so the long-term use of opiate medications is not recommend for people with ME/CFS.

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). It may be reasonable to trial an SSRI to evaluate whether there is any beneficial effect on pain or mood symptoms.

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 ME/CFS pain or Fibromyalgia where the pain mechanisms are probably different (http://www.nice.org.uk/guidance/CG173).

Migraine prophylaxis may also be beneficial and this should also be managed according to NICE guidance.

Gastrointestinal symptoms

Gastrointestinal (GI) symptoms are common in people with ME/CFS. 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 ME/CFS frequently have GI symptoms they rarely ask for help with these and GP's 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 IBSC. 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 ME/CFS. 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, sterculia 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 ME/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 ME/CFS 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 ME/CFS 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 guideline and the European task force guideline 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 and 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. 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 and prescribing of these agents should only be done by clinicians with experience of treating Autonomic Disorders.

Refer to secondary care if the orthostatic intolerance is very severe, is getting worse, or there are concerns another condition may be responsible.

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. Other medications for managing tachycardia should be guided by a specialist with experience of treating Autonomic Disorders.

Sleep disturbance

Sleep disturbance is common in patients with ME/CFS. 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.

Promethazine is another agent which could be considered at a dose of 25-50mg at night to help initiate sleep.

Mental health issues

ME/CFS is not a primary mental health condition. However, comorbid mental health problems should be treated because poorly controlled depression, anxiety disorders, obsessional compulsive disorder and post-traumatic stress disorder can significantly impact on the severity of ME/CFS symptoms. 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 ME/CFS 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 guideline
Depression: https://www.nice.org.uk/guidance/ng222
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 ME/CFS 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 effects 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 ME/CFS 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 ME/CFS 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 the 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 fexofenadine 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 ME/CFS (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.

Drug therapy will rarely be tolerated and should be avoided.

Drug Allergy/Intolerance

Patients with ME/CFS 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.

Menstrual Cycle related symptoms

Many women with ME/CFS report variation in the ME/CFS symptoms related to different stages of their menstrual cycle. This has also been recognised and studied in people with Postural Tachycardia Syndrome (POTS). Both oestrogen and progesterone have effects on the vascular system including influencing the degree of vasodilation and vasoconstriction. They can also both have effects on collagen in the body which may be a relevant factor for people who are Hypermobile. Different people report fluctuations at different times in their cycle but the commonest pattern is for ME/CFS symptoms to escalate in the pre-menstrual week.

Medications such as NSAIDS e.g. Mefenamic Acid and Tranexamic acid maybe helpful to reduce the menstrual related pain and heavy bleeding which will aggravate ME/CFS symptoms.

Puberty and the menopause

Puberty and the menopause are times when there is a greater degree of hormone fluctuation and instability and this may explain why these can be times when ME/CFS has been observed to occur more often and it can also be the time when pre-existing ME/CFS symptoms get worse. Using hormonal products such as contraceptive agents and HRT products can sometimes create better hormonal stability which may be beneficial for helping to also stabilise ME/CFS symptoms.

Menopausal fatigue can be severe enough to mimic ME/CFS and a trial of HRT might be prudent before confirming a diagnosis of ME/CFS.

Hypermobility

Oestrogen can stabilise collagen and Progestogens can loosen collagen. This can mean hypermobility related symptoms can fluctuate in response to fluctuating hormone levels. One common pattern is that the increased progesterone levels that occur pre-menstrually can mean that people with Hypermobility report increased pain symptoms in the week before their period along with increased frequency of subluxations/dislocations. Many people with Hypermobility also have reduced proprioception and some people report

becoming clumsier and more prone to accidents in the week prior to their period. Further information is available from the Hypermobility Syndromes Association website: www.hypermobility.org/hormones-and-hypermobility

Pre-Menstrual Syndrome

Many women experience fluctuating mood symptoms through their menstrual cycle and this can add an additional burden to their ME/CFS symptom fluctuations. Identifying and managing PMS can also have a beneficial effect on ME/CFS symptoms so it is important to be vigilant for it as well as the more severe form of PMS sometimes referred to as Pre-menstrual Dysphoric Disorder (PMDD). Prompting patients to keep a symptom tracking diary can help identify menstrual cycle related problems. SSRI medication used in the luteal phase of the cycle can help some women. Hormonal products can be of benefit although can also aggravate symptoms for some women. Contraceptive hormonal products which achieve hormonal stability are worth trying and if symptoms are severe, consider referral to a specialist as it may be appropriate to consider use of GnRH analogues. Further information is available from The National Association for Premenstrual Syndromes (NAPS): www.pms.org.uk

Hormone options

Products that contain oestrogen have the potential to reduce the cyclical variation in hypermobility symptoms due to the stabilising effect on collagen. Autonomic Disorders that are characterised by orthostatic hypotension may also benefit from oestrogen due to it's effect to increase Blood Pressure. Using the combined pill with 'long cycle regimes' (ie reducing the number of withdrawal bleeds by running packs together) can be a helpful way to minimise cyclical variation in symptoms.

Oestrogen use may be limited due to potential thromboembolic risks particularly in people with a personal or family history of venous clots and people who are long-term bed bound and immobile. People with a history of migraine with aura should not take contraceptive products containing ethinyloestradiol. However, HRT products which contain estradiol can be used safely in people with a history of migraine with aura. HRT products that are delivered transdermally (i.e. patches or gel) can also be considered for people with thromboembolic risk after discussion with the patient – further information regarding thromboembolic risk is available from the British menopause Society: www.thebms.org.uk/2011/05/risk-of-recurrent-thrombosis-affected-by-type-of-hrt/

Progesterone only products such as the progesterone only pill, the contraceptive implant, the Intrauterine system eg Mirena coil and Depo Provera may be useful considerations to help with cyclical symptoms in people with ME/CFS. Products with higher levels of progestogen such as the Depo injection may be less suitable for people who are hypermobile due to the risk of it increasing their musculoskeletal symptoms.

People who have Autonomic Dysfunction may be more susceptible to their BP dropping during a coil fitting procedure so this would need to be factored into the decision. If performing a coil procedure ensure the person has had adequate fluid and food intake prior to the procedure, use cervical anesthetic and have facilities on hand to manage a vasovagal

episode should it occur. For people with severe Autonomic Symptoms where an IUS is an important consideration consider referring to a gynecologist so the procedure can be done in a hospital setting.

If an IUS device on it's own doesn't fully resolve the cyclical symptoms, then it is worth considering adding in a low dose transdermal HRT estrogen patch as this can help with the cyclical vascular and mood symptoms that occur.

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 is a monoclonal antibody against CD20 bearing 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 and many haematological malignancies.
A recent publication from Norway stated that in a study they had conducted there were beneficial effects of Rituximab on ME/CFS patients. If these effects are real and can be reproduced, the findings may guide us to understanding what causes ME/CFS.

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 ME/CFS 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 emphasis 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 ME/CFS 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 and a major source is through regular sunlight exposure on the skin. Vitamin D deficiency is common in people living in the UK and people with ME/CFS may be more susceptible due to a reduced ability to do outdoor activities. Vitamin D has many important functions including regulating calcium metabolism, reducing inflammation and supporting normal neuromuscular and immune system activity. Vitamin D deficiency may contribute to fatigue and muscle aches in some people, so it is important to be vigilant for the possibility of Vitamin D deficiency and correct abnormalities when present. NHS guidance is that all adults should consider taking a 10mcg supplement throughout the winter months, someone with ME/CFS who has little daylight exposure should consider being on supplementation throughout the year.

For further information, please see the NICE guideline on Vitamin D.

Vitamin B12 IM and Folic Acid: Gastrointestinal symptoms are a common feature of ME/CFS so it is important to screen for evidence of nutritional deficiencies at the onset of fatigue symptoms and also at other periods in the illness where there is a deterioration in symptoms or there is evidence of dietary problems. Nutritional deficiencies should be corrected as per usual guidelines with consideration given to check for underlying causes of malabsorption and whether monitoring is required. There are some physicians who advocate and prescribe Vitamin B12 and folic acid for fatigue and fibromyalgia in the absence of any detectable deficiency and there is no evidence base for this approach.

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.

Conclusion

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

Many patients with ME/CFS have co-morbid conditions and these should also be managed according to best practice. It should be remembered that patients may struggle to access care because of their limited energy.

Please refer to the:

- NICE guideline on multimorbidity
- NICE guideline on thyroid disease
- NICE guideline on irritable bowel syndrome in adults.
- NICE guideline on depression in adults
- NICE guideline on depression in adults with a chronic physical health problem
- NICE guideline on depression in children and young people
- NICE guideline on generalised anxiety disorder and panic disorder in adults
- NICE guideline on common mental health problems.