MANAGEMENT FILE

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MEA membership costs £18 a year for people living in the UK/BFPO.
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the ME association

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TREATING ME/CFS – including new and experimental approaches to management

INTRODUCTION

Drugs, supplements and vitamins can be used in three different ways when it comes to treating almost any illness.

First is to cure the condition – as when an antibiotic is prescribed to quickly eradicate an acute infection.

Second is to try and modify what is called the underlying disease process – the use of powerful anti-inflammatory drugs in rheumatoid arthritis, or the use of antidepressants to treat depression, are good examples.

Third is to relieve specific symptoms such as pain or sleep disturbance – something that is often well worth trying in any disease even though the underlying cause of the symptom may not be fully understood.

When it comes to using drugs in ME/CFS, there is obviously no curative treatment at present and none on the horizon. The prospect of having a curative treatment will almost certainly have to wait until research provides us with more substantial information as to what is really going wrong in this illness.

Significant abnormalities have now been identified involving infection, immune system responses, the nervous system, muscle and mitochondrial function, and hormonal control.

These are the type of abnormalities that can be used as the basis for considering and investigating new forms of treatment which are aimed at modifying the underlying disease process.

However, until we gain a much clearer picture of the possible role of disease-modifying drugs in ME/CFS, the main use of drug treatments is going to be for the relief of common symptoms such as pain, irritable bowel and gastric symptoms and PoTS (postural orthostatic tachycardia syndrome).

Drugs and other approaches that provide symptomatic relief are already covered in separate MEA information leaflets and will not be reviewed here.

So what sort of treatments for ME/CFS have already been assessed and brought into use? How might new drugs be assessed and brought into use? And what sort of new and speculative ME/CFS treatments might become available in the future?

HOW ARE NEW DRUGS ASSESSED AND BROUGHT INTO USE?

Before a drug can be licensed for use in a specific condition like ME/CFS, and then recommended for use by NICE, there must be sound and consistent evidence of both benefit and safety from a number of 'gold standard' clinical trials. Such trials are normally carried out in what is termed a randomised, double-blind, and placebo-controlled manner.

In simple terms this means that the patients involved are divided into two matched groups. Each group is then given either a placebo or the active drug. The patients in both groups do not know which they are receiving – neither do the organisers of the trial. They are then assessed over a period of time to record side-effects and to what extent the patients taking the active drug respond in comparison to those taking the placebo.

Drug trials are extremely costly to carry out – so the assessment process often starts with small numbers and pilot studies. If the initial results are encouraging, the assessment process progresses to what is called a phase 3 clinical trial – the so-called gold standard of assessment for clinical trials.

If one or more phase 3 clinical trials can demonstrate both efficacy and safety, the drug will almost certainly be given what is called a product license and made available on the NHS. However, as we know from the Rituximab clinical trial in Norway, there can be very encouraging signs based on early observations and from small clinical trials. But when a large phase 3 clinical trial was conducted, the results

failed to confirm that Rituximab was an effective treatment for ME/CFS.

Clinical trials are clearly important but one of the problems with ME/CFS is that we have a lot of clinical and pathological sub-groups under the current umbrella. So a one-size-fits-all approach to treatment is unlikely to work.

Consequently, clinical trial analysis must also allow for the fact that there may be a small sub-group responding – even though most of the people involved are not responding.

HOW CAN WE TREAT ME/CFS?

What follows is an A-Z summary of all the treatments – drugs, supplements, vitamins and non -drug approaches – that have been assessed, are being assessed, or could be assessed to see if they could be safe and effective treatments for ME/CFS.

ACTIVITY MANAGEMENT: GRADED EXERCISE THERAPY (GET) AND PACING

In our current state of knowledge, activity management – balancing physical, mental and emotional activity with rest in a manner that is appropriate and within a person's limitations – is the most important aspect of managing ME/CFS.

Patient evidence – gained from our very detailed survey of management approaches (www.meassociation.org.uk/2015/05/23959/) – indicates that **pacing** is the safest and most effective form of activity management.

Unfortunately, we do not have any results from clinical trials that have properly assessed the benefits of pacing – although several research papers have advocated its use over and above other methods.

Conversely, **graded exercise treatment** (GET) – currently recommended by NICE for everyone with mild or moderate ME/CFS – has made the condition worse in over 50% of people with ME/CFS who were advised to try it.

GET is supported by some clinical trials. However, the largest, most influential and most recent trial, the PACE Trial, has been heavily criticised by

clinicians and researchers. This criticism will be considered when NICE reviews their 2007 guideline on ME/CFS.

While it is welcome to note that the recommendation on GET will form part of the re-assessment of evidence for the new NICE guideline, this will not appear until October 2020. And, despite requests by the ME Association to NICE for GET to be removed from the current guidance, there is no indication at present that this will happen.

We also require good quality research studies to investigate the role of activity management in ME/CFS in a way that takes account of stage, severity and fluctuation of symptoms. These sort of trials also need to include objective outcome measures (eg the use of actometers).

Health professionals would then be in a much better position to provide sound guidance on activity management.

ANTIDEPRESSANTS

Low doses of antidepressants – in particular sedating tricyclic drugs such as **amitriptyline** – can sometimes be very useful in relieving pain, improving disrupted sleep patterns, and helping with sensory symptoms. Higher doses over a prolonged period may be necessary when someone with ME/CFS also develops true clinical depression.

However, there is no evidence from clinical trials to indicate that any of the antidepressant drugs that are currently in use are an effective form of treatment for ME/CFS. In other words, they have no effect on the underlying disease process and do not restore health and function.

One possible exception is the use of a group of antidepressant drugs known as SSRIs (selective serotonin uptake re-inhibitors) – **sertraline** (trade name, Lustral) in particular. This is because there is evidence that a disturbance involving a brain chemical transmitter called serotonin occurs in some people with ME/CFS.

Anecdotal evidence indicates that some people with ME/CFS have gained benefit from using sertraline to increase the level of serotonin in the brain. However, we also know that other people with ME/CFS are very sensitive to SSRI medication and feel worse as a result.

In other words, a sub-group of people with ME/CFS appear to have low levels of serotonin and might benefit from an SSRI whereas others have normal, or elevated levels of serotonin, and are therefore very sensitive to this type of medication. So the use of an SSRI, even at a very low dose, is an approach that may be worth trying but has to be done very cautiously.

- The ME Association has a leaflet covering all aspects of depression and the use of antidepressant drugs in ME/CFS.

ANTIVIRAL DRUGS

Viral (and sometimes bacterial) infections are a very common trigger factor in the development of ME/CFS. A debate continues as to whether some of these triggering infections (enteroviral infections in particular) may then persist at a cellular level – as happens in the case of HIV or hepatitis C infection – and play a role in causing ME/CFS symptoms. However, the current balance of evidence indicates that persisting viral infection is not involved in the underlying disease process.

There is more robust evidence to indicate that some types of dormant viral infection – herpes viruses such as EBV and HHV-6 in particular – become reactivated in ME/CFS.

Two antiviral drugs have been assessed so far in clinical trials in people with ME/CFS.

A small early trial found no benefits from using **acyclovir** – a drug that is very effective at treating herpes virus infections. However, more recent trials in America carried out by Professor Jose Montoya's group at Stanford, who use **valganciclovir** (trade name, Valcyte), indicate that this antiviral drug could be of value in carefully selected patients with clinical and laboratory evidence of reactivation of HHV-6 infection.

The ME Association followed this up and met with representatives of Roche Pharmaceuticals (who manufacture Valcyte) to discuss the possibility of a UK trial. Unfortunately, the pharmaceutical company decided not to pursue this line of research.

The role of reactivated viral infection in ME/CFS, along with clinical trials that have been taking place in America involving valganciclovir, are summarised in more detail and referenced in the research and treatment sections of *ME/CFS/PVFS: An Exploration of the Key Clinical Issues* (The MEA's 'Purple Book').

AUTONOMIC NERVOUS SYSTEM DYSFUNCTION

The autonomic nervous system consists of two groups of nerves that help to control heart rate and blood pressure. There is growing evidence from research carried out by Professor Julia Newton, at the University of Newcastle, of significant autonomic dysfunction in ME/CFS, including a condition called PoTS (postural orthostatic tachycardia syndrome) in some people.

Autonomic dysfunction may help to explain why a significant proportion have abnormal blood pressure and pulse rate responses when they stand up and consequently feel faint. These findings have resulted in the assessment of drugs such as midrodine that can help to reduce the effects of autonomic dysfunction on cardiovascular responses to changes in posture.

Other research into cardiac (heart) function in ME/CFS has produced findings which may relate to both symptoms and treatment. Of particular interest here is low blood volume and the possibility that intravenous (by drip) saline therapy could be of benefit to some people with ME/CFS.

Anecdotal reports from America – where saline therapy is sometimes prescribed – indicate that it can be helpful. However, inappropriate fluid expansion can also be dangerous.

So this type of fluid replacement must be regarded as experimental at present and should only be considered where an experienced doctor is involved. It cannot be recommended more widely until clinical trials have confirmed both efficacy and safety.

- The ME Association has leaflets covering the diagnosis and management of both autonomic nervous system dysfunction and PoTS. This includes information on the various drug treatments that are sometimes prescribed for people with PoTS.

COGNITIVE BEHAVIOUR THERAPY (CBT)

CBT is the other form of treatment recommended in the current NICE guideline for the management of people with mild or moderate ME/CFS.

Like GET, this is controversial because CBT may be recommended on the basis that it can 'treat ME/CFS' through altering what are called abnormal illness beliefs and behaviours.

But a more practical form of CBT can also be used to help people cope with the consequences of having a long term physical illness – as can be the case in a number of other conditions

Patient surveys carried out by the ME Association indicate that the vast majority of people do not find that CBT is an effective form of treatment for their ME/CFS. But it can help some people to cope with emotional and psychological effects of having a long-term condition.

As with GET, the ME Association has called for CBT to be removed as an automatic recommendation for people with mild or moderate ME/CFS in the new NICE guideline. But it may have a role when it used to help coping mechanisms.

- The ME Association position on both CBT and GET is set out in more detail in the summary of our report covering patient evidence covering acceptability, efficacy and safety of CBT, GET and Pacing; **https://tinyurl.com/y4xs9qpt**
- We also have leaflets covering Activity Management, Pacing and CBT.

HORMONES

Although research has revealed that a number of hormonal abnormalities occur in ME/CFS, the evidence from clinical trials means that the use of hormonal replacement remains very speculative and, in some cases, potentially dangerous.

The hormonal abnormality that has attracted greatest attention is **hypo-**

cortisolaemia This refers to a slightly lowered level of cortisol in the blood Cortisol is a vital hormone that is produced by the adrenal glands but whose output is under the control of the hypothalamus gland in the brain.

The explanation for this abnormality remains uncertain and any form of cortisone supplementation has to be managed with great caution. This is because steroids, including cortisone, are drugs that can cause unpleasant side-effects. And once started, it may then be difficult to discontinue due to suppression of the natural output of the hormone from the adrenal glands.

Two clinical trials have assessed the value of using very low doses of **hydrocortisone** but the results were not sufficiently conclusive to recommend supplementation.

Clinical evidence published in *The Lancet* reported that the use of an **oestradiol patch and cyclical progestagen** may be of value in women who have a premenstrual exacerbation of symptoms along with low levels of plasma oestradiol (a naturally occurring oestrogen).

At present, there is no sound evidence of **thyroid gland dysfunction** (ie hypo-thyroidism) in ME/CFS, although a recently published paper has reported on an aspect of thyroid dysfunction where ME/CFS patients had relatively higher levels of another thyroid hormone called "reverse T3" or rT3.

This appeared to be due to a shift in hormone production, where the body preferred to convert T4 to rT3 instead of producing T3. The low T3 levels found in ME/CFS patients coupled with this switchover to rT3 could mean that T3 levels are severely reduced in tissue.

Some doctors are willing to prescribe thyroid supplements to people with ME/CFS. However, the use of thyroid supplements in people with normal thyroid function tests has potential dangers and cannot be recommended in our current state of knowledge, especially in people who may also have a degree of hypocortisolaemia.

Melatonin is a naturally occurring hormone that is produced by the pituitary gland in the brain. It helps to keep the 'body clock' functioning normally, especially in relation to the induction of sleep at night. We know from patient surveys (the most recent being the MEA website survey in October 2017) that a significant number of people with ME/CFS use melatonin to help sleep disturbances, especially when this is more severe.

Interestingly, the NICE guideline on ME/CFS allows for the use of melatonin in children – provided it is recommended and supervised by a paediatrician. But NICE makes no such recommendation for adults in the current guideline

Consequently, most adults find that doctors are unwilling to prescribe melatonin on the NHS and have to purchase it via the internet – which is not always a safe and reliable source for this type of treatment.

The ME Association is currently looking at the possibility of setting up a clinical trial to assess the efficacy and safety of melatonin in adults.

The use of **dehydroepiandrosterone (DHEA)** supplements is also unwise. This is because there is no sound evidence of DHEA deficiency in ME/CFS and this hormone has been linked to cancer.

- The MEA has leaflets covering the Management of the Menopause and research into female hormone status in ME/CFS, Thyroid Function and Thyroid Function Tests, and Sleep – the latter includes information on Circadin (prescription-only melatonin).

DRUGS THAT CAN MODIFY THE IMMUNE SYSTEM RESPONSE

Various markers of immune system dysfunction can be found in people with ME/CFS. These include raised levels of cytokines, abnormalities in natural killer (NK) cell function, B- and T-cell function, and the production of autoantibodies – potentially harmful antibodies that are directed against the body's own tissues, rather than infections and allergens.

A popular hypothesis here involves a triggering infection which then results in an on-going abnormality involving the body's immune defence system. One possibility, supported by recent research evidence, is that there is an on-going over-production of cytokines – chemicals that cause people to feel unwell when they have any type of infective illness.

A considerable number of immunological treatments have therefore been assessed as possible forms of treatment for ME/CFS. The list includes Ampligen, immunoglobulin (IgG) injections, alpha interferon, inosine pranobex (trade name Imunovir), rituximab, staphylococcus toxoid vaccine and tumour necrosis factor inhibitors.

Ampligen is a very expensive American drug that is claimed to have both antiviral and immunomodulatory properties. Ampligen has not been approved for use in ME/CFS by the Food and Drug Administration – the US drug regulator – and is unlikely to be made available in the UK until this approval has been given.

Inosine pranobex/Imunovir is an immunomodulatory drug that has a potential to enhance natural killer cell activity. Anecdotal reports indicate that some people find this drug to be helpful and some specialists are willing to prescribe it. Other doctors are generally unwilling to do so in view of the NICE recommendation to not use immunomodulatory drugs in ME/CFS.

Rituximab (a monoclonal anti-CD20 antibody) is an anti-cancer drug that causes depletion of B lymphoctye cells in the body. It was reported to be beneficial in a preliminary trial carried out in Norway but a further large trial failed to confirm these findings.

Tumour necrosis factor inhibitors are widely used in more severe rheumatoid arthritis to dampen down inflammation in the joints. Preliminary results from a pilot study involving six ME/CFS patients indicated that one drug in this group (etanercept) could be of benefit and needs to be tested in larger clinical trials. Another drug in this group called anakinra has also been assessed in a clinical trial in The Netherlands but there were no significant benefits.

MUSCLE ENERGY SUPPLEMENTS

Activity-induced muscle fatigue is the key clinical feature of ME/CFS and there is now sound research evidence of biochemical abnormalities in the way that the mitochondria – a core 'battery like' component part of muscle cells – produce energy in response to physical exertion. These mitochondrial abnormalities cannot be explained by simple deconditioning or inactivity.

Not surprisingly, this finding has led to the production of various muscle energy supplements, many of which are promoted by commercial supplement manufacturers, as possible forms of treatment.

Examples include carnitine, co-enzyme Q10, creatine, magnesium, NADH (nicotinamide adenine dinucleotide) and D-ribose. Some of these supplements have been assessed in small clinical trials but the results are not impressive.

Based on this research evidence, the only one that may be worth trying is **carnitine**. These clinical trails are summarised in more detail, and referenced, in *ME/CFS/PVFS: An Exploration of the Key Clinical Issues* .

A number of commercial supplements, often containing multiple contents, are being promoted to people with ME/CFS on the basis that they can improve mitochondrial function and/or energy production. There is no evidence from clinical trials that these products are effective. The ME Association does not therefore endorse their use.

- The MEA has a separate leaflet covering the four most common Muscle Energy Supplements.

NERVOUS SYSTEM STIMULATION

A case report and a small trial have assessed the use of **modafinil** (brand name, Provigil).

Modafinil is a drug that stimulates the central nervous system and so helps to reduce daytime sleepiness and improve mental alertness in narcolepsy and sleep apnoea.

One trial described how modafinil was of considerable benefit in one person with severe ME/CFS. However, the more recent placebo-controlled trial involving 14 patients queried its value.

Methylphenidate, another type of nervous system stimulant, has also been assessed in a clinical trial but cannot be recommended for individual use. The drugs bible for doctors – the *British National Formulary* – does not recommend the use of central nervous system stimulants for patients with fatigue.

VITAMINS, MINERALS AND SUPPLEMENTS

There is no sound evidence of significant deficiency in ME/CFS of any of the main common vitamins, including vitamin B12 in ME/CFS.

This means that vitamin supplements are probably unnecessary – unless there are significant dietary restrictions. Taking large doses of over-the-counter single vitamin supplements can also cause serious side-effects and is not recommended.

One important exception is that some people with ME/CFS are at risk of developing **Vitamin D deficiency** – especially those who are housebound and/or on restrictive diets.

So vitamin D supplementation should be discussed with a doctor if you are at increased risk of vitamin D deficiency due to a lack of sunlight on the skin (the main way in which vitamin D is produced). People with moderate or severe ME/CFS, and are mainly or totally housebound, can have their vitamin D level checked with a simple blood test.

Uncertainties and controversy surround the use of **vitamin B12** in ME/CFS. The NICE guideline does not recommend the use of any vitamin treatments but some doctors are willing to try vitamin B12.

This is not on the basis that people with ME/CFS are deficient in vitamin B12, or any sound research evidence. It is based on the theory that vitamin B12 supplementation could help to improve nervous system repair.

Before considering this form of treatment, it is important to make sure there is no evidence of pernicious anaemia being present. The ME Association is looking at the possibility of funding a clinical trial to assess the use of vitamin B12 injections.

There are theoretical reasons why treatment with **essential fatty acids** (such as Efamol Marine) and **eicospentaenoic acid (EPA)** could be of benefit in ME/CFS. The results from clinical trials are conflicting in the case of Evening Primrose Oil (EPO). For EPA, a small clinical trial described some benefit, especially for improving cognitive function. EPA appears to a safe supplement to use and it may just be worth a try for a month or two – if you can afford the cost.

Folic acid deficiency has been reported – so folic acid supplementation should always be discussed with a doctor, especially by anyone who is intending to get pregnant, or is pregnant.

Probiotics can be helpful in some cases of irritable bowel syndrome where this co-exists with ME/CFS. If research into the possible role of the microbiome in ME/CFS (the viruses and bacteria that inhabit the gut) identifies clear abnormalities, the use of specific probiotics could become more widespread.

- The MEA has separate Management Files on EPO and EPA, Vitamin supplements, Vitamin B12 and vitamin D. The Management File on Irritable Bowel Syndrome symptoms covers the use of probiotics and dietary modification.

OTHER DRUGS

Other speculative forms of treatment include **low-dose naltrexone** (an opiate/morphine antagonist) and **nimodipine** (a drug that may help to increase blood supply to the brain).

One small clinical trial has indicated

that low dose naltrexone could be of benefit in fibromyalgia – a condition involving widespread pain that can co-exist with ME/CFS. No clinical trials have taken place using nimodipine, or any other drug in this category that dilates blood vessels.

Results from a clinical trial published in 2004 found no benefit from the use of **galanthamine hydrobromide** – a selective acetyl cholinesterase inhibitor that has been used to treat cognitive decline in people with dementia.

Researchers in Norway, who carried out the Rituximab trial, have also been carrying out a trial involving the use of **cyclophosphamide**. This is a drug with powerful anti-inflammatory effects and is used in conditions like rheumatoid arthritis when other drugs fail to work. But it can also cause serious side-effects. Results from this trial should be announced later in 2018.

- A report on this trial can be found in issue 144 (Spring 2018) of the MEA'S membership magazine *ME Essential*.

PRESCRIBING NEW AND EXPERIMENTAL FORMS OF DRUG TREATMENT

All the supplements referred to in this Management File can be obtained from pharmacies, health food stores and internet suppliers.

The drug treatments can only be obtained on prescription. However, most doctors are going to be reluctant or unwilling to prescribe drugs they are unfamiliar with and that have not been licensed or approved or recommended for use in a specific illness.

This is partly because if anything goes wrong as a result of side-effects, a doctor could then be sued by a patient if he/she has been using an unfamiliar drug that has not yet been licensed for the treatment of ME/CFS – even where a patient initially stated that they would take responsibility for any adverse effects.

An additional obstacle to using speculative forms of treatment is the current (2007) NICE guideline on ME/CFS.

This guidance recommends that doctors should not prescribe a number of categories of drugs – including antiviral medication, immune system modulators, nervous system stimulants, steroids, and thyroxine. The NICE guideline also concluded that there is insufficient evidence to justify prescribing any of the widely used vitamins and supplements described in this summary.

On a more positive note, NICE has accepted that the current guideline is not meeting the needs of people with ME/CFS and that it needs to be re-written. Hopefully, this will result in a new guideline that allows clinicians to make more use of their clinical judgement, especially in relation to the use of antiviral and immunomodulatory drugs.

LOOKING TO THE FUTURE

As we learn more about the underlying disease processes in ME/CFS, it might be possible on a much more experimental level to assess other 'cutting edge' treatments and preventative measures.

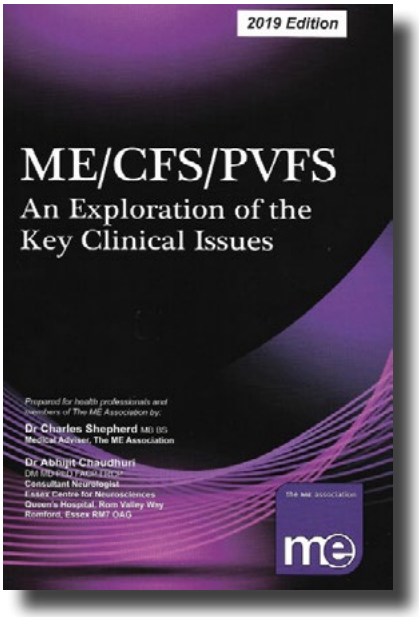
Examples might include:

- Autologous bone marrow transplants – where cells are removed from a person before they receive high-dose chemotherapy or radiation treatment. After high-dose chemotherapy or radiation treatments, the stems cells are put back in the body to make normal blood cells. This approach is now being used in the treatment of some forms of blood cancer.
- Stem cell therapy – which is now being assessed as a way of repairing damaged neurons in conditions like multiple sclerosis and Parkinson's disease.
- Faecal microbiome transplants (FMT) – if research involving the microbiome indicates that there are significant changes in gut microbiology in ME/CFS. Dr Peter Johnsen and colleagues in Norway have recently reported positive results from a clinical trial which used FMT in the management of irritable bowel syndrome. They are now planning to do a similar trial in ME/CFS. Pubmed reference to the IBS study: https://www.ncbi.nlm.nih.gov/pubmed/29100842
- Vaccination against specific i nfections, such as Epstein Barr virus/ glandular fever, that are common trigger factors for ME/CFS.

FURTHER INFORMATION

If you or your doctor require further information, or references to the use of any of these treatments in ME/CFS, these can be found in the treatment and reference sections of the 2019 edition of our clinical and research guide: *ME/CFS/PVFS: An Exploration of the Key Clinical Issues.*

- Please let us know if you are using any of these experimental and speculative forms of treatment and what effect they are having.



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