LONG COVID AND ME/CFS

Are they the same condition?

MAY 2023

THE ME ASSOCIATION

LONG COVID AND ME/CFS - ARE THEY THE SAME CONDITION?

The ME Association has been providing information and support to people with Long Covid since May 2020 when it became apparent that significant numbers of people were not recovering from COVID-19 infection.

They were developing a post-Covid syndrome that became known as Long Covid and which often included symptoms that are the same as ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome). In some cases people with Long Covid were meeting diagnostic criteria for ME/CFS.

Since then we have continued to cover all aspects of Long Covid on our social media - where we regularly report on research and treatment developments.

This is a review of the key clinical and causative overlaps that occur between Long Covid and ME/CFS.

The review also explains how our existing knowledge about the management of post-viral fatigue, cognitive dysfunction/brain fog, orthostatic intolerance, postural orthostatic tachycardia syndrome/PoTS, pain management and unrefreshing sleep in ME/CFS can also help people with the same symptoms where they occur in Long Covid.

1. BACKGROUND

It is estimated that around 10% of people who catch COVID-19 infection are failing to fully recover and have what has been termed Long Covid (or the post COVID-19 syndrome). This is a diagnosis that is normally made when a person is still symptomatic 3 months after the onset of an infection where there is good clinical evidence that it was caused by COVID-19. Having a positive COVID-19 test is helpful but not essential.

At present, there is no diagnostic blood test for either Long Covid or ME/CFS. The process of diagnosis is very similar for both conditions. This requires three months of symptoms along with the exclusion of other possible explanations.

The ME Association (MEA) takes the view that Long Covid and ME/CFS are both examples of a serious and debilitating condition that can follow any type of viral infection. And while a wide range of viral (and sometimes non-viral) infections can trigger ME/CFS, in previous coronavirus infection outbreaks (e.g. SARS/severe

Long Covid and ME/CFS - Are they the same condition? was written by Dr Charles Shepherd, Trustee and Hon. Medical Adviser to The ME Association.

DISCLAIMER

We recommend that the medical information in this leaflet is discussed with your doctor. It is not intended to be a substitute for personalised medical advice or treatment. You should consult your doctor whenever a new symptom arises, or an existing symptom worsens. It is important to obtain medical advice that considers other causes and possible treatments. Do not assume that new or worsened symptoms are solely because of ME/CFS.

acute respiratory syndrome in 2002-2004 and MERS/Middle East Respiratory Syndrome in 2012) there were reports in the medical literature of some people going on to develop an ME/CFS-like illness.

Both conditions have some key symptoms in common and there may be a similar level of fluctuating functional impairment in both. However, there are some important differences that distinguish some people with Long Covid from those with ME/CFS.

There is also an increasing number of people who have had Long Covid, or symptoms suggestive of Long Covid, who are now being diagnosed with post-COVID ME/CFS.

While research is taking place into all aspects of Long Covid, we are only just beginning to understand the complexities of this condition. We clearly need research studies that compare all aspects of Long Covid and ME/CFS to see where there are similar disease processes involved.

Given the many overlaps between trigger factors, symptoms and causative mechanisms, research into Long Covid could well provide useful information relating to both the cause and treatment of ME/CFS

■ The NICE rapid guideline – Managing the long-term effects of Covid-19 – outlines the current recommendations for symptom recognition, diagnosis, and management for Long Covid:

https://tinyurl.com/3fdxxf64

We clearly need research studies that compare all aspects of Long Covid and ME/CFS to see where there are similar disease processes involved.

2. EPIDEMIOLOGY

How many people have Long Covid?

At present, we have no firm indication as to how many people have been diagnosed with Long Covid. Self-reporting data collected by the Office of National Statistics (see below) indicates that around 1.7 million people are still symptomatic three months after their initial infection here in the UK. Worldwide, it has been estimated that there could be around 65 million people with some form of Long Covid.

With ME/CFS, research has estimated a prevalence range of between 0.2 – 0.4% of the population - which means that up to 250,000 people in the UK could be affected. However, we don't have any accurate or up to date information on the number of people diagnosed with ME/CFS. The true figure is probably significantly higher.

Here are the most recent data (March 30th 2023) on Long Covid from the Office of National Statistics:

- An estimated 1.9 million people living in private households in the UK (2.9% of the population) were experiencing self-reported long COVID (symptoms continuing for more than four weeks after the first confirmed or suspected coronavirus (COVID-19) infection that were not explained by something else) as of 5 March 2023 (see Figure 1).
- Of people with self-reported long COVID, 83,000 (4%) first had (or suspected they had) COVID-19 less than 12 weeks previously, 1.7 million people (92%) at least 12 weeks previously, 1.3 million (69%) at least one year previously and 762,000 (41%) at least two years previously.
- Of people with self-reported long COVID, 545,000 (29%) first had (or suspected they had) COVID-19 before Alpha became the main variant; this figure was 247,000 (13%) in the Alpha period, 327,000 (17%) in the Delta period and 698,000 (37%) in the Omicron period.
- Long COVID symptoms adversely affected the day-to-day activities of 1.5 million people (79% of those with self-reported long COVID), with 381,000 (20%) reporting that their ability to undertake their day-to-day activities had been “limited a lot”.
- Fatigue continued to be the most common symptom reported as part of individuals’ experience of long COVID (72% of those with self-reported long COVID), followed by difficulty concentrating (51%), muscle ache (49%) and shortness of breath (48%).
- As a proportion of the UK population, prevalence of self-reported long COVID was greatest in people aged 35 to 49 years, females, people living in more deprived areas, those working in social care, teaching and education or health care, and those with another activity-limiting health condition or disability.

ONS Source:

https://tinyurl.com/4uajk9xe

Although the ONS statistics include people who are still unwell four weeks after an infection, a diagnosis of Long Covid is normally based on a person still having symptoms at three months from the onset of the infection.

AN ME ASSOCIATION SUMMARY OF
THE 2021 NICE CLINICAL GUIDELINE FOR ME/CFS

ESSENTIAL INFORMATION
FROM THE NEW NICE GUIDELINE

DECEMBER 2021

NICE National Institute for Health and Care Excellence

The ME Association is delighted that the guideline has been published and we fully support the recommendations that it contains.

The ME Association has produced a free booklet summarising the NICE clinical guideline that can be downloaded here:

https://meassociation.org.uk/istd

At the ME Association, most of the people with Long Covid that we have been helping over the past three years have been previously healthy adults in their 20s to 50s (with some being athletically very fit) who were often self-managed at home during their initial COVID-19 infection. Current research suggests that around 90% of people with Long Covid were managed at home and around 40% never had any NHS care.

We are also aware of a growing number of children and adolescents with Long Covid. The most recent study looking at the prevalence in school-age children reported a prevalence estimate of 1.8% for primary schoolchildren aged 4 – 11 years, 4.5% for secondary schoolchildren aged 11 – 16 years, and 6.9% for secondary schoolchildren aged 16 – 18 years.

Research reference:

https://tinyurl.com/yjfnkyrb

We are also aware of a growing number of children and adolescents with Long Covid

3. RISK FACTORS FOR LONG COVID AND ME/CFS

In addition to having an infectious trigger, both ME/CFS and Long Covid have a significant female predominance – possibly related to the fact that they both have an autoimmune component.

Other risk factors that are emerging for Long Covid include asthma, obesity, living in a deprived area, and poor pre-pandemic health and disability.

The most effective way of reducing the incidence of Long Covid is to prevent people catching COVID-19 infection in the first place. Vaccination against COVID-19 is producing a significant decrease in the risk of developing Long Covid if someone does still contract the infection.

There is also some emerging evidence to show that treatment of an acute infection with the antiviral drug Paxlovid (nirmatrelvir and ritonavir) reduces the risk of developing Long Covid. So there is a strong case for prescribing this drug – when a person at increased risk catches COVID-19. Sadly, this is not the case at present.

Research reference:

https://tinyurl.com/yk8jz8z5

4.1. SYMPTOM SIMILARITIES BETWEEN LONG COVID AND ME/CFS

Long Covid has a number of common symptoms that overlap with a post-viral fatigue syndrome (PVFS) or ME/CFS.

So a significant proportion of people with Long Covid have one or more of a cluster of symptoms that are consistent with a diagnosis of PVFS or ME/CFS.

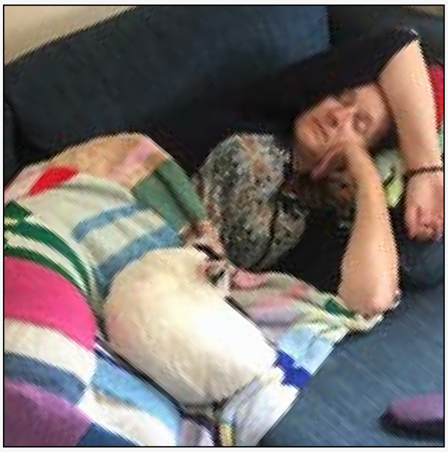
These include:

- debilitating physical and mental fatigue that is activity-induced, is exacerbated by exercise, and is not relieved by rest
- myalgia/muscle pain, arthralgia/joint pain and/or nerve pain/ neuropathic pain
- flu-like symptoms and feeling generally unwell
- cognitive dysfunction (‘brain fog’) – problems with short-term memory, concentration, attention span, information processing and retrieval
- dysautonomia - problems with regulating heart rate and blood pressure during changes in posture leading to orthostatic intolerance (difficulty in remaining upright) and postural orthostatic tachycardia syndrome/PoTS (a significant rise in pulse rate when moving from lying/sitting to standing resulting in dizziness or feeling faint)
- sleep disturbance which may include both hypersomnia (increased sleep requirements) and insomnia (poor quality sleep). Sleep is often described as ‘unrefreshing’
- headaches
- poor temperature control – sensitivity to both hot and cold environments
- sensory disturbances – e.g. paraesthesiae (‘pins and needles’)
- post-exertional malaise/symptom exacerbation – in which there is a worsening of symptoms after activity. This is often delayed in onset by hours or days, is disproportionate to the activity, and has a prolonged recovery time that may last for hours, days or weeks. Research studies indicate that a significant proportion of people with Long Covid experience post-exertional malaise.

A significant proportion of people with Long Covid have one or more of a cluster of symptoms that are consistent with a diagnosis of PVFS or ME/CFS

Disabling fatigue is often the main or a very prominent symptom in Long Covid. While it has a lot of similarities to the fatigue that occurs in ME/CFS, damage to the lungs (where there may be problems with oxygen transfer from the lungs to the blood vessels) and heart (where there may be damage to the heart muscle or conducting systems) may be exacerbating an underlying post-viral fatigue in people with Long Covid.

As with ME/CFS, symptoms often fluctuate from day to day and from week to week. Some symptoms increase or decrease in severity whereas others remain static, and new symptoms may appear as time goes on.



Disabling fatigue is often the main or a very prominent symptom in Long Covid

4.2. SYMPTOM DIFFERENCES BETWEEN LONG COVID AND ME/CFS

A significant proportion of people with Long Covid also have a layer of symptoms that are directly related to involvement of their lungs, heart and blood vessels, liver, kidneys, brain and nervous system, gastrointestinal tract, or skin that occurred at the time of the original infection and which caused damage to or affected the function of these organs.

The more common Covid-specific symptoms include:

- shortness of breath and/or cough
- chest pains
- heart-rhythm disturbances/cardiac arrhythmias
- palpitations on exertion
- periodic fevers
- loss or change of taste (parosmia) and/or smell
- abdominal pain and diarrhoea – which may represent a post Covid irritable bowel syndrome, or an inflammatory bowel syndrome:

https://tinyurl.com/y6smeexb

- skin rashes - including ‘Covid toe’
- hair loss

Skin rashes, including ‘Covid Toe’ are amongst the symptoms of Long Covid, but this is not seen in ME/CFS

As COVID-19 can affect almost every organ in the body, a much wider range of symptoms has been reported in Long Covid than in ME/CFS. In some cases, these Covid-specific symptoms predominate. In other cases, they are combined with ME/CFS-type symptoms in varying degrees. The mix of symptoms may change over time in relation to both type and severity.

Symptoms involving mental health - anxiety, depression, even post-traumatic stress disorder/PTSD – can also occur, as in ME/CFS. In some cases of Long Covid the mental health symptoms dominate the clinical picture.

A diagnosis of Long Covid does not require the presence of the very significant (ie 50% or more) functional impairment relating to physical and mental activity that is required to confirm a diagnosis of ME/CFS.

4.3. THE OVERALL CLINICAL PICTURE

To summarise:

A significant proportion of people with Long Covid have symptoms that are directly related to their COVID-19 infection (e.g. shortness of breath, chest pains, loss of taste or smell) and often have some ME/CFS-type symptoms.

A smaller group of people with Long Covid have an illness that is dominated by COVID-19 specific symptoms and have no significant component involving ME/CFS-type symptoms.

A further group have an illness that is dominated by ME/CFS-type symptoms and few or no symptoms that are directly related to COVID-19. In this case a diagnosis of Post-Covid ME/CFS may be more appropriate if they meet with diagnostic criteria for ME/CFS.

Two research studies from America have reported on the number of people with Long Covid who meet with ME/CFS diagnostic criteria. This varied between 40% and 60%.

Research references for Long Covid cases also meeting diagnostic criteria for ME/CFS:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9998690/

https://www.mdpi.com/2035-8377/15/1/1

DIAGNOSIS OF ME/CFS

THE IMPORTANCE OF HAVING AN
EARLY AND ACCURATE DIAGNOSIS

APRIL 2022

The MEA has an information booklet that covers all aspects – clinical history, examination, blood tests - of the diagnosis of ME/CFS in more detail:

https://meassociation.org.uk/mwta

5.1 WHAT CAUSES LONG COVID?

In addition to the overlapping symptoms, there are some important overlaps as to what may be causing both ME/CFS and Long Covid.

Predisposing factors: In both cases there may be a genetic predisposition. Genome-wide association studies, including the DecodeME study, are now in progress to see if people who develop both Long Covid and ME/CFS have genetic factors that increase susceptibility and response to infections.

Precipitating factors: While Long Covid has, by definition, to date back to a definite COVID-19 infection, the situation with ME/CFS is that it can be triggered by a wide range of viral infections and occasionally non-viral infections. Other types of immune system stressor – such as vaccinations – can also occasionally trigger ME/CFS.

Perpetuating factors: Three separate components appear to be involved in maintaining Long Covid symptoms.

- First is damage to organs that occurred at the time of the infection – the heart and lungs in particular – and which have not resolved.
- Second are factors that appear be involved in the causation of other post-viral syndromes such as ME/CFS - in particular immune system dysfunction involving low-grade immune system activation and autoantibody production, neuroendocrine dysfunction involving the hypothalamic-pituitary-adrenal axis, endothelial dysfunction and mitochondrial dysfunction.
- Third is an area of much uncertainty and the possibility that some other pathology is involved – such as persisting viral infection or the formation of small blood clots/micro-clots.

At a scientific level we don't fully understand why many people with Long Covid (and ME/CFS) experience such a dramatic fall in energy levels and why they are unable to undertake any form of strenuous physical activity, or sustain any form of physical or mental activity. As this fatiguability affects both brain and muscle function, it's possible that there are problems involving both the brain and muscle, and possibly the immune system. So it is good to see that some of the research into Long Covid, which could be helpful in relation to ME/CFS, is looking at the way in which infection, brain and muscle could all be involved.

Research reference:

https://tinyurl.com/yeym9fvu

> "I have had long Covid for three years. Even though I have made huge progress I still suffer most days with chronic pain in my joints, a rolling sense of vertigo, fatigue and brain fog. To look at me you might think I'm fine, but it is achingly painful that I can't physically manage the activities I used to enjoy"
>
> LUCY ADAMS, BBC NEWS

5.2. IMMUNE SYSTEM INVOLVEMENT

5.2.1 Cytokines: One very interesting overlap between Long Covid and ME/CFS is the involvement of immune system chemicals called cytokines – which cause inflammation and many of the flu-like symptoms that are associated with any acute infection.

During the acute stage of COVID-19 there can be what is termed a cytokine storm – with a massive over-production of cytokines causing inflammation in the lungs and serious respiratory complications. There is also research evidence in ME/CFS to indicate that an on-going cytokine response involving what are called pro-inflammatory cytokines fails to 'switch off' after the initial triggering infection.

Cytokines can then pass through what is called the blood-brain barrier and affect an area of the brain called the hypothalamus (which acts as a thermostat for temperature control along with appetite, sleep and hormone regulation), and control centres in the brain for the autonomic nervous system (which controls heart rate and blood pressure during changes in posture and leads to orthostatic intolerance and PoTS).

There is now research evidence of a similar type of cytokine-mediated immune system activation in Long Covid to the one that has already been found in ME/CFS:

https://tinyurl.com/2exmrfp3

A combination of infection entering the brain, along with an on-going immune system response, could lead to activation of structures called microglia and even demyelination (loss of the protective covering) of message-carrying neurons. This has been put forward as one possible explanation for the cognitive dysfunction that occurs in Long Covid - as well as in ME/CFS.

The Scientist news report:

https://tinyurl.com/mr3s9scx

5.2.2 Autoimmunity: There is growing evidence that another component of the immune system response in Long Covid involves the production of autoantibodies – these are potentially harmful antibodies that are directed against the body's own tissues.

One very interesting overlap between Long Covid and ME/CFS is the involvement of immune system chemicals called cytokines – which cause inflammation and many of the flu-like symptoms that are associated with any acute infection.

Low levels of autoantibodies are also sometimes found in ME/CFS. And while not confirming that ME/CFS (or Long Covid) is what would be termed an autoimmune disease, this finding does suggest that there is an autoimmune component.

Research reference:

https://tinyurl.com/2jyk3v99

5.3. CENTRAL NERVOUS SYSTEM INVOLVEMENT?

Research carried out in Oxford, which has investigated brain changes in 785 participants from the UK Biobank before and after catching COVID-19, has reported a decrease in grey matter volume and brain damage in areas that are involved with the detection of smell.

Changes in both grey and white matter volume have also been demonstrated using structural neuroimaging techniques in people with ME/CFS. This is another finding that could help to explain cognitive dysfunction in both ME/CFS and Long Covid.

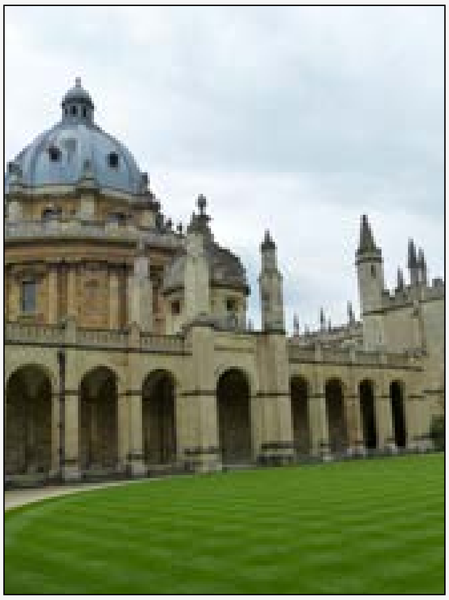
Research paper in Nature:

https://www.nature.com/articles/s41586-022-04569-5

A magnetic resonance imaging study from Australia has found similar abnormalities in brainstem volume in both Long Covid and ME/CFS

Research reference:

https://tinyurl.com/25vj8war



Research carried out in Oxford has reported a decrease in grey matter volume and brain damage in areas that are involved with the detection of smell.

5.4. ENDOCRINE INVOLVEMENT

As with ME/CFS, there is evidence of suppression of the hypothalamic-pituitary-adrenal axis and hypocortisolaemia (reduced output of cortisol from the adrenal glands). While this is not the severe reduction in cortisol levels that are found in Addison’s disease, it could play a role in symptom production.

Research reference:

https://tinyurl.com/be2phwht

5.5. ENDOTHELIAL DAMAGE AND BLOOD CLOTS

Damage to the endothelium, the cellular structure that lines the inside of all blood vessels, has been suggested as another possible cause of Long Covid. This may link in with the persisting formation of small blood clots (micro-clots) in tiny blood vessels called capillaries.

There is now a substantial amount of research evidence that people with COVID-19, and in some cases of Long Covid, have complications relating to the formation of both large and small blood clots.

While there is research evidence of endothelial dysfunction in ME/CFS, there is no sound evidence of this type of blood clotting problem in small blood vessels. Given the lack of clinical evidence for clotting complications occurring in ME/CFS, it therefore seems unlikely that blood clotting abnormalities are involved the pathology of ME/CFS.

Research reference:

https://tinyurl.com/yc4mwu26

Some cases of Long Covid, have complications relating to the formation of both large and small blood clots.

5.6. PERSISTING VIRAL INFECTION?

A reservoir of persisting viral infection in the gastrointestinal tract has been suggested with one research group concluding that COVID-19 can infect gastrointestinal tissue and is associated with gastrointestinal symptoms.

Research reference:

https://tinyurl.com/2bj347nd

The presence of viral particles in other tissues has also been put forward. A US study, involving 44 autopsies from people who had died from COVID-19 infection, detected persistent SARS-CoV-2 RNA in multiple anatomic sites, including throughout the brain, as late as 230 days following symptom onset in one case. Despite extensive distribution of SARS-CoV-2 RNA throughout the body, they observed little evidence of inflammation or direct viral cytopathology outside the respiratory tract. Their data indicates that in some patients SARS-CoV-2 can cause systemic infection and persist in the body for months.

https://tinyurl.com/ut7uaffk

COVID-19 can infect gastrointestinal tissue and is associated with gastrointestinal symptoms.

5.7. REACTIVATION OF CHRONIC VIRAL INFECTION

Evidence of reactivation of chronic viral infections such as Epstein-Barr virus, as has been found in ME/CFS, is now being reported in Long Covid.

Research reference:

https://tinyurl.com/2fzxfsu5

Reactivation of chronic viral infections such as Epstein-Barr virus, as has been found in ME/CFS, is now being reported in Long Covid.

5.8 MITOCHONDRIAL DEFECT IN ENERGY PRODUCTION

As with ME/CFS, there is evidence of mitochondrial dysfunction in Long Covid – the mitochondria playing a crucial role in the energy production at a cellular level. It is interesting to note that a sustained impairment in cardiopulmonary exercise testing has been found in both ME/CFS and Long Covid.

Research reference:

https://tinyurl.com/3jfhp23x

5.9. SKELETAL MUSCLE PATHOLOGY

A small study involving sixteen patients with Long Covid who complained of fatigue, myalgia, or weakness reported histological changes in all subjects. Muscle fibre atrophy was found in 38%, and 56% showed indications of fibre regeneration. Mitochondrial changes - comprising loss of cytochrome c oxidase activity, sub-sarcollemmal accumulation, and/or abnormal cristae - were present in 62%.

Research reference:

https://tinyurl.com/2s3k2df3

5.9. MICROFLORAL DYSBIOSIS

There is preliminary evidence of changes to the composition of the natural bacterial and viral population in the intestines – as has been reported in ME/CFS. Given the interaction between the gut microbiome, the central nervous system and the immune system, this finding may be linked to immune system dysregulation in both conditions.

Research reference:

https://tinyurl.com/a4f4facm

COVID-19 vaccines appear to be producing a significant improvement in symptoms in some people with Long Covid, but can exacerbate symptoms in people with ME/CFS.

5.10. THE ROLE OF COVID VACCINES

One important difference between Long Covid and ME/CFS is the way in which COVID-19 vaccines appear to be producing a significant improvement in symptoms in some people with Long Covid – possibly as a result of 'resetting' the abnormal immune system response. However, in ME/CFS, vaccinations are a well-recognised factor in causing an exacerbation of symptoms in some people, and only rarely cause improvement.

Research reference:

https://tinyurl.com/2amsfs9b

6. ASSESSING AND DIAGNOSING LONG COVID

Management of Long Covid should consist of carefully assessing people to check if there is any clinical and laboratory evidence of on-going damage (which may be permanent) or dysfunction (which may or may not improve over time) involving the lungs, heart, liver, kidneys, etc. This information can then be used to provide appropriate guidance on the management of individual symptoms relating to this type of organ damage or dysfunction.

What is becoming clear is that basic screening tests such as chest X-rays, standard scans and ECGs are not always the most effective way of picking up the sort of subtle lung and heart damage/dysfunction that can occur in Long Covid, and that sophisticated scanning techniques may provide far more useful information.

LONG COVID AND ME/CFS -
ARE THEY THE SAME CONDITION?

A multi-center pilot study carried out in the UK, which used Xenon-gas MRI scans to measure oxygen transfer from lungs to blood vessels, has reported some significant defects in people with Long Covid that would not be found using more standard tests of lung function.

BBC news report:

https://tinyurl.com/4nkft8bm

Differential diagnosis: As with ME/CFS, it is important to make sure that other possible explanations for Long Covid symptoms are considered. There is a real danger, partly due to problems with accessing face-to-face medical appointments, that any form of continuing ill health following COVID-19 is diagnosed as Long Covid.

Consideration should, for example, be given in women over the age of 40 who may be/are going through the peri-menopause (the transitional period before the menopause) or the menopause as to whether some of their symptoms are due to the menopause and falling levels of oestrogen and could be helped by the use of HRT. A similar situation occurs in ME/CFS.

The possibility that COVID-19 has destabilised a pre-existing medical condition, or precipitated symptoms in a condition that has not yet been recognised, must be also considered.

Conditions such as diabetes, coeliac disease, inflammatory bowel disease, polymyalgia rheumatica, and sleep apnoea can be misdiagnosed as Long Covid when patients are not being properly assessed. There have also been several reports of people with a malignancy being initially diagnosed as having Long Covid.

Misdiagnosis can be reduced by following the same sort of rigorous clinical assessment process, including a range of baseline blood tests, that should always occur when ME/CFS is being queried or diagnosed. These tests are described in the MEA publication covering Early and Accurate Diagnosis (see section 4.3).

Investigation of Covid specific symptoms involving the lungs, heart, kidneys, etc are outside the scope of this review. However, consideration should certainly be given to including tests such as:

- D-dimer - as a marker of blood coagulation
- Brain natriuretic peptide – if there is any suggestion of heart failure
- Pulse oximetry – to assess tissue oxygenation

Misdiagnosis can be reduced by following the same sort of rigorous clinical assessment process, including a range of baseline blood tests.

7.1 TREATING LONG COVID

At present, there is no safe and effective drug treatment for Long Covid. As with ME/CFS, it's highly unlikely that we are ever going to find a single successful 'magic bullet' treatment for every person who has Long Covid.

However, a number of drug treatments are now being assessed in clinical trials and it may be that treatments that provide some help to some people with Long Covid will eventually emerge.

The MEA has approached clinicians involved in some of these clinical trials to see if it might be appropriate to also include a group of people with ME/CFS.

Examples of some of drugs that are attracting interest because they may also be helpful in ME/CFS include:

Ampligen (rintatolimab) - an experimental drug that has immunomodulatory and antiviral properties and which has been assessed for use in ME/CFS

Clinical trial reference:

https://tinyurl.com/2sbn4r7f

AXA 1125 is another experimental treatment that aims to improve mitochondrial (muscle energy) function. A clinical trial is currently in progress in Oxford.

MEA website news item on AXA1125 dated 3 November 2021:

https://tinyurl.com/2ta77nkf

Results from a phase 2 placebo-controlled clinical trial that was carried out in Oxford were published in The Lancet in April 2023. These results indicate that whilst AXA 1125 produced some improvement in self-reported fatigue in some patients with Long Covid there was no objective evidence of improved mitochondrial function - which was the primary outcome measure.

If further work demonstrates that this is an effective treatment for Long Covid then a trial involving ME/CFS needs to be done and the MEA Ramsay Research Fund would be very keen to receive a proposal involving ME/CFS.

Research reference:

https://tinyurl.com/ytds34ek

A number of drug treatments are now being assessed in clinical trials and it may be that treatments that provide some help to some people with Long Covid will eventually emerge.

Apheresis is a technique that removes disease-causing components from the blood. This rather controversial approach is being assessed in private clinics in Germany and some other European countries. The research into blood clotting forms the basis of the so-called micro-clot model. This proposes that small clots in the blood capillaries prevent oxygen from reaching the tissues and are a basic cause of Long Covid. Consequently, this clotting abnormality could be treated with anti-clotting drugs.

MEA website news item on apheresis dated 26 October 2021:

https://tinyurl.com/yc4e8uxw

Anticoagulant therapy: On the basis that Long Covid may involve fibrin amyloid micro-clots and platelet activation micro-clots in the capillaries, a study involving the use of triple anticoagulant therapy - involving clopidogrel, aspirin and apixaban plus a proton pump inhibitor/pantoprazole - has been reported some benefits.

Whilst these results are obviously interesting, they need to be viewed with considerable caution as there was no control group (in a condition where a significant proportion of people are improving) and no objective measures of outcome. This is a treatment that also has the potential to cause serious side-effects. Anticoagulation is not therefore a form of treatment that should be used until consistent evidence of benefit and safety is confirmed in well-conducted clinical trials.

Clinical trial paper:

https://tinyurl.com/53uxrvap

Antihistamines: Another interesting therapeutic development is the finding that some people with Long Covid have symptoms of what is called mast cell activation syndrome – where a viral infection destabilises mast cells causing the release of histamine. Where this occurs there are reports that treatment with drugs called histamine H1 and H2 receptor antagonists (e.g. cetirizine and famotidine) and a low-histamine diet can be helpful.

Probiotics: As dysbiosis can affect people with Long Covid (and ME/CFS), researchers in Cambridge have carried out a clinical trial involving a pre- and probiotic supplement. They reported benefits in both gastrointestinal and non-gastrointestinal symptoms.

https://tinyurl.com/3jz5a4ke

Other approaches involving drug treatment being assessed in clinical trials include:

- **Colchine** to reduce inflammation
- **Hyperbaric oxygen therapy** – where results from a small UK study reported potential benefits:

  https://tinyurl.com/3ukjpuvu
- **Low-dose naltrexone** – where a clinical trial is being funded by the Canadian Institute of Health Research:

  https://tinyurl.com/ysahppah
- **Paxlovid** – an antiviral drug that is effective against COVID-19 infection and which may reduce the risk of Long Covid when an infection occurs:

  https://tinyurl.com/2xvz7bdn

  https://tinyurl.com/5t53hhwv
- **Stellate ganglion block** – on the basis that this procedure could recalibrate the fault in the autonomic nervous system and improve cerebral/brain blood flow:

  https://tinyurl.com/3dfess3x
- **Transcutaneous vagal nerve stimulation** - another potential treatment aimed at recalibrating the fault with the autonomic nervous system

  https://tinyurl.com/38cvex2h

7.2. SYMPTOM MANAGEMENT

For symptoms that are the same as those found in ME/CFS, the same sort of self-help management strategies and symptomatic relief involving drugs should be discussed with a health professional. The MEA has information leaflets covering all aspects of symptom management that overlap with Long Covid.

Cognitive dysfunction/brain fog:

https://tinyurl.com/yvcdwxhc

Dysautonomia – orthostatic intolerance and PoTS:

https://tinyurl.com/yc5u9rt2

https://tinyurl.com/yp47z526

Gastrointestinal symptoms:

A variety of gastrointestinal problems are often reported in Long Covid and conditions such as inflammatory bowel disease and coeliac disease should be considered. The type of symptomatic management used in irritable bowel syndrome should also be considered. The MEA has an information leaflet covering the management of IBS-type symptoms where they occur in ME/CFS:

https://tinyurl.com/22jsftbd

Pain:

https://tinyurl.com/s5x3h4uf

The MEA also has information leaflets covering the use of specific drugs such as low-dose amitriptyline, gabapentin and pregabalin for pain relief in ME/CFS.

Sleep and restless legs syndrome:

https://tinyurl.com/4nye84tn

For Covid specific symptoms there is good support and information available from other medical charities:

Breathing and lung problems – British Lung Foundation:

https://tinyurl.com/4b95ddee

Loss of taste and/or smell:

https://tinyurl.com/mr24hh8p

https://tinyurl.com/mry5wy28

The MEA has produced a review of treatments that are currently being assessed for Long Covid:

https://tinyurl.com/59pfuxk7

2023 review of clinical trials for Long Covid:

https://tinyurl.com/rkhrphdz

Politico review of Long Covid treatment trials:

https://tinyurl.com/yswpb8st

7.3. ACTIVITY AND ENERGY MANAGEMENT

Most people with Long Covid have a type of debilitating fatigue and inability to sustain physical and mental activities that is very similar or identical to that which occurs in ME/CFS.

Symptoms will often worsen both during and in the days following increased physical activity or exercise that is going beyond what a person can comfortably cope with. This is known as post-exertional malaise (PEM) or post-exertional symptom exacerbation and is a key diagnostic feature of ME/CFS.

As with ME/CFS, it is important to note that physical activity is different to exercise. Physical activity is any muscle movement that requires the production of energy. Exercise is a planned, structured and intentional movement that aims to maintain or to improve strength or cardiovascular fitness. Graded exercise, which involves incremental increases in activity, is sometimes recommended for people who have become inactive and deconditioned after an injury or illness.

The cause of fatigue in ME/CFS is complex and probably involves abnormalities in energy production and management at a central (brain) and peripheral (muscular) level. From the research findings so far, it appears that this may be occurring in Long Covid as well. The type of fatigue seen in ME/CFS and Long Covid is not caused by deconditioning.

The ME Association therefore recommends pacing - the type of activity and energy management that is used in ME/CFS – for people with Long Covid who are experiencing debilitating fatigue.

We do not recommend graded exercise therapy (GET) - as there is a real risk of harm if inappropriate graded exercise programmes are prescribed to people with both ME/CFS and Long Covid. NICE issued a statement of caution in 2020 about the use of GET in Long Covid after myself and Dr William Weir expressed our concerns:

https://tinyurl.com/4ucfjxez

The aim of pacing is to find a stable baseline of activity and avoid 'doing too much' on one day and then feeling unable to do anything the next, due to increased levels of fatigue and other symptoms. Once the situation has stabilised any increase in physical or mental activity needs to be gradual and flexible and allow for the fact that progress is still likely to be erratic.

The ME Association recommends pacing - the type of activity and energy management that is used in ME/CFS – for people with Long Covid who are experiencing debilitating fatigue.

Pacing of both physical and mental activity is the most important way of avoiding post-exertional malaise and providing the groundwork for improvement to occur.

The section on activity and energy management at pages 28-32 in the new NICE guideline on ME/CFS is also very helpful here:

https://tinyurl.com/47u58wpr

7.4. EDUCATION AND EMPLOYMENT

Not surprisingly, there are high rates of Long Covid in people who are/were employed in the health service, social care, the teaching professions, hospitality, retail and transport. So they require information and guidance on the sort of modifications to hours, duties, travel, etc that will need to be made if/when someone has reached the point where a phased or modified return to education or employment is possible.

Unfortunately, it is becoming clear that many people with Long Covid are experiencing the same sort of practical and discriminatory problems that occur in ME/CFS when it comes to obtaining reasonable adjustments and modifications where they are still able to participate in some form of employment or education.

Long Covid was not listed as a named disability in the 2010 Quality Act. But the fact is that some people with Long Covid clearly have an illness that is causing a significant and long-term reduction in their ability to carry out normal daily activities, which is likely to remain in place for a year or more. This means that under the Act they should be classified as being disabled in relation to the modifications and reasonable adjustments required to enable them to perform normal routines at work, school or college.

There has now been a case where it was ruled that the person with Long Covid did meet criteria for inclusion under the 2010 Equality Act:

https://tinyurl.com/2hknm3p3

The MEA has a new information booklet covering activity and energy management and pacing:

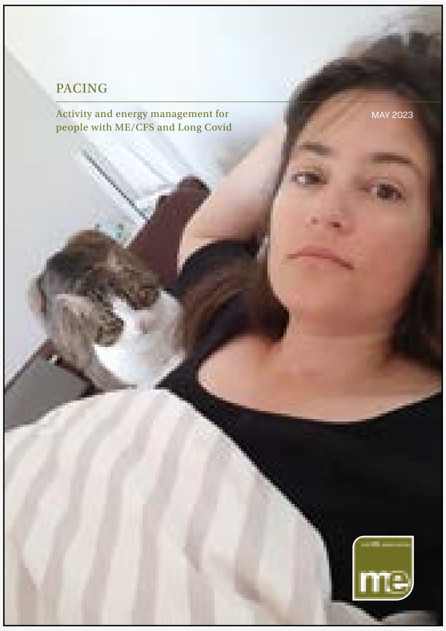
https://meassociation.org.uk/me-association-shop/

EMPLOYMENT ISSUES & ME/CFS

DECEMBER 2022

The MEA has produced a booklet on employment issues and ME/CFS. This may also be helpful for people with Long Covid:

https://meassociation.org.uk/vo36



PACING

Activity and energy management for people with ME/CFS and Long Covid

MAY 2023

7.5. LONG COVID CLINICS

There is now a network of around 90 hospital-based Long Covid clinics where adults can be referred by their GP. There are also 14 clinics for children and adolescents. As with referral services for ME/CFS, these NHS clinics are mainly in England with only a small number of Long Covid services in Northern Ireland, Scotland and Wales.

Data on demographics indicates that referrals are heavily weighted towards white females between the age of 35 and 64 and that many people from deprived communities are not being referred.

Feedback to the MEA indicates that these clinics are often very good at assessing people for damage to the lungs, heart and other organs that may have been affected by the initial infection, but not so good at having the necessary time to spend on personalised management.

Many of these services also lack the necessary expertise to deal with ME/CFS-type symptoms.

So some people with Long Covid are being helped by a package of pulmonary (lung) rehabilitation, appropriate activity and energy management programmes and (if required) the psychological support that many of the Long Covid clinics provide.

Some people with Long Covid are being helped by a package of pulmonary (lung) rehabilitation, appropriate activity and energy management programmes and (if required) the psychological support that many of the Long Covid clinics provide.

However, some of the Long Covid referral services are not being open-minded about all the different and possible causes of Long Covid - especially the fact that a significant proportion of people with Long Covid have post-exertional malaise and meet with other diagnostic criteria for ME/CFS. Consequently, they seem unwilling to accept that activity and energy management involving convalescence and pacing is going to be far more helpful than a ‘one size fits all’ approach that can be based on graded exercise.

We continue to be surprised and disappointed that some of the the Long Covid referral services are not making use of information on management of key symptoms - especially debilitating fatigue, cognitive dysfunction, dysautonomia, pain and sleep disturbance - that are common to almost any serious post-viral disease state.

There have been proposals to establish joint Long Covid and ME/CFS clinics in some parts of the UK. The MEA position is that they should normally be kept separate at present - due to the need to have specialist input for the heart and lung problems in Long Covid - but to establish links to ME/CFS clinics so patients can be referred for help with management of ME/CFS type symptoms.

One such joint service has now opened in the Isle of Man – where there are good geographical and population reasons for setting up a joint service and the MEA has been helping with its development.

7.6. NICE GUIDELINES ON LONG COVID AND ME/CFS

The NICE rapid guideline – Managing the long-term effects of Covid-19 – outlines the current recommendations for symptom recognition, diagnosis, and management for Long Covid:

https://tinyurl.com/5n8jtbaf

There is also a new NICE guideline covering the diagnosis and management of ME/CFS. People with Long Covid may find that the recommendations on energy and symptom management here are more helpful than in the Long Covid guideline.

https://www.nice.org.uk/guidance/ng206

Research studies are now starting to report on prognosis in Long Covid and have found that most people were still significantly unwell one year on following the infection.

8. PROGNOSIS - WHAT HAPPENS TO PEOPLE WITH LONG COVID?

The overall outlook in Long Covid appears to be very uncertain – as with ME/CFS.

Many people are finding that their condition fluctuates in severity – often more dramatically than occurs in ME/CFS. Some people stabilise and improve whereas others deteriorate and now have a more severe form of Long Covid. While some people are clearly improving, those who achieve a full, sustained recovery from Long Covid appear to be in a minority.

Research studies are now starting to report on prognosis in Long Covid. A report from the University of Leicester PHOSP COVID study, which is looking at people who were treated in hospital, found that most were still significantly unwell one year on following the infection.

Reference:

https://www.leicesterbrc.nihr.ac.uk/phosp-covid-one-year/

A study from France on 968 people with Long Covid who had mainly been managed at home reported that 85% were still symptomatic one year after the onset of symptoms.

Research reference:

https://tinyurl.com/44v5435c

9. HOW CAN THE ME/CFS MEDICAL AND PATIENT COMMUNITY HELP THOSE WITH LONG COVID?

The MEA has been trying to build bridges with the Long Covid patient and medical communities by providing information and guidance on the management of symptoms that overlap with ME/CFS.

This includes using ME Connect and our social media platforms to provide information and support to people with Long Covid with increasing numbers of people with Long Covid joining in discussions on MEA Facebook – where they are very welcome.

This collaboration has not been helped by some members of the Long Covid patient community being misinformed that ME/CFS is a psychological illness and not therefore wanting to acknowledge any possible connection or collaboration.

Many health professionals and researchers also have very limited or inaccurate knowledge about ME/CFS and are not aware of management guidance and research findings in ME/CFS that may well be relevant to Long Covid.

10. HOW CAN RESEARCH INTO LONG COVID HELP PEOPLE WITH ME/CFS?

This interaction with the Long Covid patient and medical communities should be a two-way process given all the funding and interest into the cause and treatment of Long Covid that is occurring. The MEA is therefore trying to encourage research that also includes people with ME/CFS in studies that are looking at both causation and treatment of Long Covid.

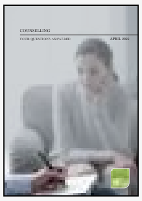
In particular, we are very keen for this research to start making use of blood samples from people with ME/CFS, multiple sclerosis and healthy controls that are available for research purposes at the ME Biobank. The MEA Ramsay Research Fund would be happy to consider research-funding proposals here.

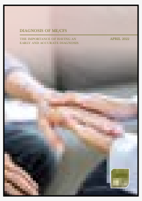
BECOME A MEMBER

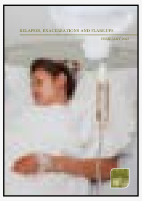
For a small subscription you can receive quarterly issues of ME Essential magazine, keep updated with the latest information on ME/CFS and with stories from other members of the charity.

You don't have to be personally affected by ME/CFS to join the ME Association. Membership is available to carers, family members, and anyone with a professional interest in the condition.

Visit our website to find out more: **https://meassociation.org.uk/8cjm**





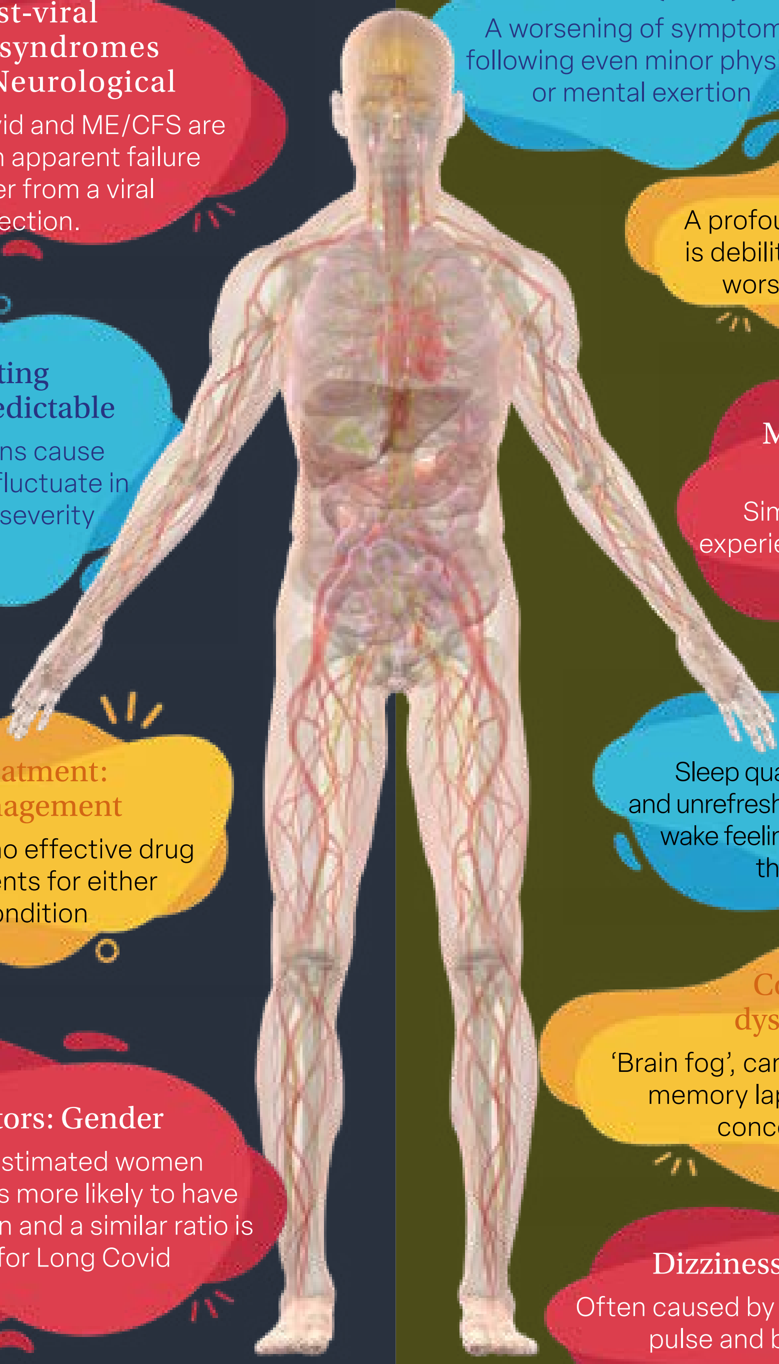


The MEA website shop:

The ME Association has the largest selection of ME/CFS advice leaflets in the UK on: Medical Management; Mental Health; Diet & Nutrition; General Information; Fundraising Leaflets; Benefits & Social Care; 'To Whom It May Concern' letters; and leaflets written by ME Connect: **https://meassociation.org.uk/shop**

LONG COVID AND ME/CFS

What do Long Covid & ME/CFS have in common?



SIMILARITIES

Post-viral fatigue syndromes (PVFS): Neurological

Both Long Covid and ME/CFS are caused by an apparent failure to recover from a viral infection.

Fluctuating illness: Unpredictable

Both conditions cause symptoms that fluctuate in intensity and severity

Treatment: Management

There are no effective drug treatments for either condition

Risk factors: Gender

It has been estimated women are up to 4 times more likely to have ME/CFS than men and a similar ratio is emerging for Long Covid

THE ME ASSOCIATION

me

KEY SYMPTOMS IN COMMON

Post-Exertional Malaise (PEM)

A worsening of symptoms following even minor physical or mental exertion

Fatigue

A profound exhaustion that is debilitating in nature and worsened by activity

Muscular aches and pains

Similar to the myalgia experienced with infections like the Flu

Sleep

Sleep quality is often poor and unrefreshing, meaning people wake feeling as bad or worse than before

Cognitive dysfunction

'Brain fog', can include short-term memory lapses, difficulty in concentrating…

Dizziness and nausea

Often caused by problems regulating pulse and blood pressure

Bowel and bladder

Many people report irritable-bowel-type symptoms such as a change in bowel habits

LONG COVID & ME/CFS

The ME Association believes that Long Covid (Post-acute Covid-19) and ME/CFS (Myalgic Encephalopathy/ Encephalomyelitis) can generally be viewed as examples of post-viral syndromes or post-infectious fatigue syndromes..

But while they share symptoms in common and can cause similar functional impairment, some people with Long Covid are experiencing symptoms that are caused by organ damage and will require additional support from medical specialists.

What do Long Covid & ME/CFS have in common?

■ Post-viral fatigue syndromes (PVFS): Neurological:

PVFS is recognised as a neurological disease by the World Health Organisation, NHS, and UK Government. ME/CFS is included in this definition. Both Long Covid and ME/CFS are caused by an apparent failure to recover from a viral infection. Long Covid is triggered by Covid-19 and its variants and c.80% of ME/CFS cases are triggered by viral infections such as Glandular Fever (Epstein-Barr virus).

■ Fluctuating illness:

Unpredictable: Both conditions cause symptoms that fluctuate in intensity and severity, and an illness that can follow a pattern of relative remission and relapse. For some the illness can get progressively worse until a period of relative stability is obtained. Both can cause significant functional impairment affecting cognition, mobility, and a person's ability to perform everyday tasks. Employment and education are likely to be affected.

■ Treatment:

Management: There are no effective treatments for either condition. Both have NICE clinical guidelines, but the Long Covid guideline is not as detailed or helpful in terms of ongoing management advice and support. NHS England has been commissioned to provide secondary care specialist services (clinics) for Long Covid and for ME/CFS. They are tasked with diagnosis, triage, and delivering personalised management advice that should be based around a technique known as 'pacing'. Provision of services in Wales, Northern Ireland, and Scotland is virtually non-existent with patients having to negotiate ongoing care and support with primary care (GPs).

■ Risk factors:

Gender: It has been estimated women are up to four times more likely to have ME/CFS than men and a similar ratio is emerging for Long Covid. Such gender imbalances also occur in autoimmune conditions. The explanation is uncertain but may be due to genetic abnormalities and the way that a woman's immune system responds to viral infections and/or hormones. Medical attitudes towards illnesses that are seen as being 'women's diseases' can be dismissive and cause a delay in diagnosis or misdiagnosis – it can also make it harder for men to receive appropriate care and support.

Key Symptoms in Common

■ Post-Exertional Malaise (PEM):

A worsening of symptoms following even minor physical or mental exertion. There is often a delay in symptom exacerbation of 12 to 48 hours. This exacerbation can last for days or weeks and lead to relapse.

■ Fatigue:

A profound exhaustion that is debilitating in nature and worsened by activity. It is not relieved by rest and is a constant symptom for most people that prevents them from initiating or completing daily tasks. It can impact mobility and exacerbate other symptoms like sleep quality and cognitive dysfunction.

▶

■ Muscular aches and pains:

Similar to the myalgia experienced with infections like the Flu, it is often constant and intrusive. It can cause disruption to sleep and periods of rest. It is a symptom that can be exacerbated by activity and exercise.

■ Sleep:

People will experience periods when they need to sleep more than is normal often when their illness is in an acute phase or during periods of relapse when other symptoms are at their worst. But sleep quality is often poor and unrefreshing, meaning people wake feeling as bad or worse than before. Sleep can also be interrupted by an inability to enter deep sleep, or by night sweats, insomnia, and bad dreams (night terrors) that lead to poorer quality sleep that is of shorter duration.

■ Cognitive dysfunction:

'Brain fog'. Symptoms can include short-term memory lapses, difficulty in concentrating or sustaining attention, difficulty with processing incoming information (reading, listening) and retrieving stored information, trouble finding the right word, remembering, mixing up commonly used words, problems with carrying out everyday tasks that involve any form of sustained mental activity.

■ Dizziness andnausea:

Often caused by problems regulating pulse and blood pressure. The body is unable to supply sufficient blood quickly enough to the brain, which can cause dizziness and nausea. It can be diagnosed as orthostatic intolerance or Postural Orthostatic Tachycardia Syndrome (PoTS). People will find these symptoms occur when trying to stand from a prone position. They will often be unable to remain standing and it can lead to fainting. It is important to get these symptoms checked and properly diagnosed as there are treatments available.

■ Bowel and bladder:

Many people report irritable bowel-type symptoms such as a change in bowel habits – diarrhoea and/or constipation – an increased or urgent need to go to the toilet, abdominal pain, bloating, a feeling of incomplete bowel evacuation; and non-bowel symptoms that might include backache, gynaecological problems, and an increased need to pass urine including when asleep.

■ 'Flu-like':

Many people describe the symptoms they experience with ME/CFS and Long Covid as being 'flu-like' in nature. These include recurrent sore throats, headaches, and the muscular aches and pains, fatigue, sleep problems, nausea, and cognitive dysfunction described above. Some people with Long Covid are reporting significant and periodic spikes in body temperature. This is not something that occurs in ME/CFS and if it does it should be properly investigated to exclude another infective illness. ■

11. FURTHER INFORMATION

MEA position statement on the overlaps between Long Covid and ME/CFS:

https://tinyurl.com/yexvx8ay

Blog on the overlaps between ME/CFS and Long Covid for Evidence Based Nursing:

https://tinyurl.com/2p98e5tb

Article for the BMA/BMJ publications with contributions from Drs Nina Muirhead, David Strain, Amy Small and myself also covers the ME/CFS and Long Covid overlap:

https://tinyurl.com/5n6nz5jf

General reviews:

Nature review of Long Covid and the overlaps with other post-infection syndromes, including ME/CFS:

https://tinyurl.com/5frn73jv

Choutka J et al. Unexplained post-acute infections syndromes. Nature Medicine 2022, 28, 911 – 923:

https://tinyurl.com/2p8p2a8b

Davis H et al. Long COVID: major findings, mechanisms and recommendations. Nature reviews microbiology 2023, 21, 133-146:

https://tinyurl.com/34emnwn9

Wong TL and Weitzer D. Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) - A Systemic Review and Comparison of Clinical Presentation and Symptomatology. Medicina 2021, 57(5), 418:

https://tinyurl.com/ch5byw4m