MEA Summary Review: Assessing PEM (Post-exertional malaise)

By: Charlotte Stephens 25th March 2019

Introduction

Post-exertional malaise (commonly referred to as PEM) is considered a hallmark characteristic of ME/CFS. However, it is not a requirement in many of the different diagnostic criteria.

There is currently no agreed upon definition of PEM, nor a formal assessment for its measurement, but creating one could improve future diagnosis of the disease.

Dr Melvin Ramsay – the clinical champion of M.E. and founding member of the ME Association – originally described what has since become known as PEM, as:

> "Muscle fatigability whereby, even after a minor degree of physical effort, three, four, or five days, or longer, elapse before full muscle power is restored and constitutes the sheet anchor of diagnosis."
>
> "Without it I would be unwilling to diagnosis a patient as suffering from ME, but it is most important the stress the fact that cases of ME of mild or even moderate severity may have normal muscle power in remission."
>
> The Saga of the Royal Free Disease (50th Anniversary Reprint).

Since then the definition of PEM has expanded, but no single version or means of assessment has really prevailed (see References for recent research on this topic).

However, in recent years we have witnessed the development of objective evidence that supports PEM as a real and unique symptom.

Latest Research

Earlier this month Professor Lenny Jason and his team from the Center for Community Research at DePaul University in Chicago, published results of a large public survey on PEM.

They hope the analysis will lead to a definitive definition and will ultimately provide a validated clinical assessment tool.

In this review, we hope to explain what PEM is, cover some of the research surrounding it and give an overview of the results from this latest research.

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Key Points

- PEM is generally regarded as a delayed exacerbation of symptoms following even mild exertion (physical or mental).
- It has been objectively demonstrated in research studies and can be used to distinguish ME/CFS from other conditions, such as MS and depression.
- The latest research study found that 98% of respondents experienced PEM and determined that creating a way to assess this characteristic feature would be a great diagnostic aid in clinical and research settings.

Defining PEM

Post-exertional malaise (PEM) is a delayed worsening of symptoms that occurs after minimal physical or mental activity.

It has also been called ‘Post-exertional neuroimmune exhaustion’ (PENE).

The key feature of PEM is that the malaise (extreme fatigue and flu-like symptoms) and other symptoms experienced are not in proportion to the amount of activity that has been done.

PEM is often delayed and may be experienced hours or days after the activity took place but is most likely to occur 1-2 days after the exertion event (Hotlzman *et al*., 2019).

This delay can lead clinicians and patients to believe that symptom exacerbations are random and unrelated to a trigger as they do not attribute their worsened condition to something that may have happened days earlier.

The effects of PEM can last for hours, days, weeks or even months. Prolonged periods of PEM are often referred to as ‘crashes’ by patients and PEM can even trigger relapse.

The exact cause and mechanisms of PEM are not yet fully understood, though a simple explanation might be that it occurs when a person with ME/CFS has gone outside of their ‘energy envelope’.

This energy envelope is described as the amount a person can safely do without triggering an increase in symptoms and/or symptom severity. PEM is triggered when available energy has been expended and they have gone into ‘energy debt’.

PEM is one of the main features that sets ME/CFS apart from other diseases and explains why exercise can be very damaging in ME/CFS, setting patients back for days, weeks or months.

The National Academy of Medicine (NAM) published a widely-cited and popular report on ME/CFS in 2015. They concluded, there was “sufficient evidence that PEM is a primary feature that helps distinguish ME/CFS from other conditions.”

Despite this, a clear definition and assessment of PEM is yet to be established.

Differing Definitions

While many acknowledge PEM as a cardinal symptom of ME/CFS, not all of the current case definitions include PEM as a diagnostic criterion (Brown and Jason 2018).

For example, although listed as one of the symptoms, the Fukuda criteria does not require PEM for a diagnosis, whereas the CCC (Canadian Consensus Criteria) does.

Some even believe that PEM is not just a clinical feature but *the* hallmark of M.E. and that it distinguishes M.E. from '*chronic fatigue*' (Twisk, 2015) and even *chronic fatigue syndrome*.

There are even suggestions of two different types of PEM. One of generalised fatigue, and the other of muscle-specific fatigue (McManinmen *et al*., 2016), and as originally described by Dr Melvin Ramsay (see Introduction).

No clear definition of PEM currently exists and its meaning can be ambiguous and misunderstood by clinicians and researchers. This is perhaps why it is often not strictly required for a diagnosis of ME/CFS in a clinical or research setting (Chu *et al*., 2018).

The National Institutes of Health/Center for Disease Control and Prevention (NIH/CDC) PEM working group attempted to define PEM as:

> An abnormal response to minimal amounts of physical or cognitive exertion that is characterized by:
> 1. Exacerbation of some or all of an individual study participant's ME/CFS symptoms.
> 2. Loss of stamina and/or functional capacity.
> 3. An onset that can be immediate or delayed after the exertional stimulus by hours, days, or even longer.
> 4. A prolonged, unpredictable recovery period that may last days, weeks, or even months.
> 5. Severity and duration of symptoms that is often out-of-proportion to the type, intensity, frequency, and/or duration of the exertion.

Unfortunately, many medical professionals still do not believe that PEM exists and instead explain the exacerbated symptoms following activity as a result of deconditioning (lack of muscle strength and overall fitness due to reduced movement as a result of incapacity).

PEM Triggers

- **Physical activity**
  Depending on severity, physical triggers can range from for example, sitting up in bed, brushing hair, brushing teeth, showering, cooking, cleaning, taking a short walk, etc.
- **Mental activity**
  Things that require concentration and memory, such as reading, mental calculation, writing, using a computer, tablet or smart-phone.
- **Social activity**
  Interacting with people either in person, on the phone or online.
- **Emotions**
  Any activity that is likely to cause heightened emotion can be a potential trigger, for example, excitement, anger, frustration, fear, grief, guilt.
- **Sensory experience**
  Sensory sensitivities are regarded as a symptom and can range from intolerances to noise, light, touch, and even to changes in the weather or certain foods and medications.
- **Stress**
  The emotions that stress can generate as well as the hormonal changes it triggers in the body.

PEM Symptoms

Increased or new symptoms experienced during an episode of PEM may include:

• ‘Brain-fog’ • Burning sensation on skin • Chronic pain (muscular or joint) • Cognitive dysfunction • Disturbed sleep pattern (lack of sleep or need to sleep too much often incl. vivid dreams) • Eye symptoms • ‘Flu-like’ feelings • Headaches and Migraines • Heaviness in the limbs or whole body • Heightened sensitivity to sensory stimuli (sound, light, smells) • Increased chronic fatigue • Loss of appetite • Loss of stamina/ functional capacity • Muscle fatigue and weakness • Nausea • Night sweats or chills • Orthostatic intolerance/dizziness • Problems regulating temperature (and cold/hot extremities) • Heart palpitations • Speech problems • Temporary paralysis • Short-term memory problems • Sore throat • Swollen and painful glands • Tinnitus (ringing in the ears) • Trembling/ instability of muscle and/or limbs • Word-finding problems

Managing PEM

As we do not yet know the underlying mechanisms of PEM, we cannot treat the cause.

Many describe PEM as 'an illness within an illness' and so addressing this would improve the quality of life of people with ME/CFS.

However, for now, most people with ME/CFS accept that PEM is part of the illness burden and resort to management strategies where possible.

These can be used in order to try and ameliorate the symptoms of PEM and include avoiding known triggers while carefully managing activities, with an approach known as 'Pacing'.

Pacing can help a person with ME/CFS understand illness-defined limitations and learn to live within these confines.

It helps to conserve energy and teaches how to avoid exceeding the 'energy envelope' until such time as health may permit. Pacing should be personalised and flexible (Goudsmit *et al*., 2012; Jason *et al.,* 2013; O'Connor *et al*., 2019).

The ME Association 2019 clinical and research guide contains a large section on illness management, and you can also find a leaflet that explains Pacing and energy management in the website shop. The website also carries information about all aspects of ME/CFS.

Heart-rate Monitors

Using a heart rate monitor to help pace activities has been found to be useful and is mentioned as a management tool in the current NICE clinical guideline on ME/CFS.

The ME Association does not recommend Graded Exercise Therapy as a management approach for ME/CFS because it is inappropriate and potentially harmful.

However, a suitable device can help with pacing to ensure people with ME/CFS stay under a certain heart rate (known as their anaerobic threshold) for as much time as possible while prompting them to rest when this limit is exceeded.

- A recent blog from Bruce Campbell has more suggestions on pacing with a heart-rate monitor that might be helpful.

Research on PEM

Several studies have shown differences in cognitive function, immune activation, gene expression, and pain inhibition before and after physical exertion in ME/CFS.

These differences are not present in healthy controls and could be used to demonstrate the existence and physiological effects of PEM (Cook *et al.,* 2017; Meyer *et al.,* 2013; Nijs *et al.*, 2014, Oosterwijick *et al.,* 2010).

Objective Measures

Most notably, PEM can be objectively shown by recording performance in a 2-day cardiopulmonary exercise test (CPET).

Patients with ME/CFS display a significant drop in their V02 max and maximal workload measures on the second day that is not seen in healthy controls or in other diseases (Hodges *et al*., 2018; Stevens *et al*., 2018; VanNess *et al*., 2010).

It has also been demonstrated that PEM symptoms are exacerbated following mental exertion alone, through the use of a cognitively challenging task (Aroll *et al*. 2014).

A recent study funded by the ME Association Ramsay Research fund showed that problems with the autonomic nervous system (ANS) may also play a role in PEM:

> Reduced parasympathetic reactivation during recovery from exercise is associated with the dysfunctional exercise-induced analgesia in ME/CFS.
>
> Poor recovery of diastolic blood pressure in response to exercise, with blood pressure remaining elevated, is associated with reductions of pain following exercise in ME/CFS, suggesting a role for the arterial baroreceptors in explaining dysfunctional exercise-induced analgesia in ME/CFS patients.
>
> (Oosterwijck *et al.,* 2017)

Clinical Assessment of PEM

Several research groups have been attempting to better define, as well as create a tool to assess, PEM.

While CPET testing as a measure of PEM has high validity and reliability, the testing itself is very costly. It can also be impractical, inconvenient and potentially harmful to patients.

Therefore, self-report data, such as questionnaires, seem to be the most practical and realistic assessment tool at this time. But until recently, there had been no validated means of determining PEM in patients with ME/CFS.

The NIH/CDC PEM working group recommended that PEM be diagnosed using a two-step process. The first step was to include five PEM items from the DePaul Symptom Questionnaire (DSQ) – an already validated and widely-used diagnostic instrument – and the second step would involve the clinician evaluating these responses in light of other information – such as previous medical records, other patient-reported scales; to reach at a final determination.

Of the five items from the DSQ, PEM duration – in which exertion had prolonged effects lasting 14-24 hours or more after exertion – was the most effective in differentiating ME/CFS from MS (multiple sclerosis) and PPS (post-polio syndrome) (Cotler *et al.*, 2018).

The importance of language and phraseology used in self-report questionnaires became apparent in earlier studies by Professor Lenny Jason and his team. For example, some questions focused on ‘feeling tired after exercise’, however, exercise is not something that all patients are capable of achieving, and so the question prompted incorrect responses.

The recent development of the ‘DePaul Post-Exertional Malaise Questionnaire’ was based on input from hundreds of patients (Jason *et al.* 2018). The questionnaire’s validity was tested independently, and it was determined that it should be used to confirm the presence of PEM in ME/CFS (Cotler *et al.* 2018).

Why is assessing PEM important?

It has been estimated that up to 91% of those affected by ME/CFS are undiagnosed or misdiagnosed. In addition, 48% of clinicians do not feel confident about making a diagnosis of ME/CFS (Chu *et al.* 2018).

Therefore, creating a tool to accurately assess PEM would improve diagnostic reliability as it is a feature that distinguishes it from other conditions (Jason *et al*., 2016).

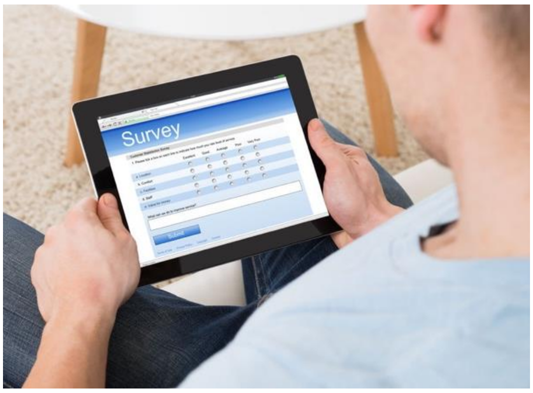
The recent and very influential National Academy of Medicine report into ME/CFS specifically highlighted the urgent need to develop simple and practical medical history, questionnaire, or physical examination items that could be used at the bedside to quickly and accurately diagnose ME/CFS.

Accurate diagnosis of ME/CFS is also important in a research setting as well as in clinical practice. Assessing whether PEM is experienced could help when recruiting patients for research studies.

This is of importance as one study found that self-reported PEM was significantly related to inflammatory and cell-mediated immune biomarkers. Furthermore, PEM can be used to make a distinction between those with ME/CFS and the more common '*chronic fatigue*' (Maes *et al.* 2012).

Latest Research Results

Previous efforts to document the actual experience of PEM and then to properly assess this characteristic symptom and to develop a diagnostic tool, have not been successful.



The latest research from Professor Lenny Jason and his team at DePaul University in Chicago, attempted to rectify the situation with a large-scale online patient survey.

Although there have been a few recent surveys with the same aims, this is by far the largest carried out to date, with over 1500 respondents from 35 different countries.

This online questionnaire built on previous work by this productive team who had developed the 'DePaul PEM questionnaire'. Instead of attempting to create an assessment tool for PEM based on their own knowledge and that taken from literature, the authors decided to work collaboratively with the patient community in order to create a more accurate and appropriate assessment tool.

> The current study involved a community-based participatory research process in an effort to develop a comprehensive PEM instrument, with critical patient input shaping the item selection and overall design of the tool.
>
> A survey was ultimately developed and was subsequently completed by 1534 members of the patient community. The findings of this survey suggest that there are key domains of this symptom, including triggers, symptom onset, and duration, which have often not been comprehensively assessed in a previous PEM instrument.
>
> This study indicates that there are unique benefits that can be derived from patients collaborating with researchers in the measurement of key symptoms defining ME and CFS.
>
> Jason et al. 2019.

Here are some of the key results from this recent research:

- 98% of participants said they experience post-exertional exhaustion and symptom exacerbation after going beyond their energy limits.
- The highest reported triggers in addition to physical/cognitive exertion were emotional events (88%), noise (85%), and sensory overload (84%).
- 85% said there were some instances in which the specific trigger of PEM could not be identified.
- 45% of respondents said that basic activities of daily living lead to symptom exacerbation most or all of the time.
- The majority of respondents (53%) reported that they experienced symptom exacerbation 1-2 days after exertion.
- The most common symptom experienced was “Reduced stamina and/or functional capacity”, followed by “physical fatigue” and “cognitive exhaustion”.
- Interestingly, over half (58%) of respondents said that they experienced ‘adrenaline surges’ during or after going beyond energy limits.
- Over half the participants (58%) said PEM lasts on average 3–6 days, with 1–2 days (39%), 1 week–1 month (47%), and 1–6 months (30%) also being frequently reported.
- 67% of participants had experienced a “crash” that never resolved.
- Only 6% felt that pacing completely allowed them to avoid PEM, while the majority reported pacing only being effective some of the time and only at a moderate/mild level.

Limitations

It should be noted that a level of selection/recruitment bias is likely present in this latest research, as is often the case with voluntary online questionnaires.

This means that the people who chose to participate in the questionnaire may have been more likely to experience PEM and that is why they chose to be involved.

This could potentially lead to an over-representation of the proportion of people with ME/CFS who experience PEM.

Additionally, 347 participants had 'incomplete surveys' and so were not included in the results. These could have potentially represented people who did not experience PEM and so didn't feel they could answer the questions.

Furthermore, the questionnaire only included those who had access to the internet and who came across the survey online, again restricting the study pool to the existing ME/CFS online community.

Finally, those that were able to complete the questionnaire may underrepresent the more severely affected patient, the newly diagnosed and those without a current diagnosis.

Conclusion

PEM remains an important characteristic symptom of ME/CFS that could help with diagnosis, but an accurate assessment tool needs to be developed that can be used in clinics and in research.

It is a symptom that can be objectively determined as being distinct from other medical conditions such as Multiple Sclerosis and Post-Polio Syndrome.

Until such time as the objective measuring devices can be made available in clinics and more appropriate for all severities of ME/CFS, we must depend on the development of accurate subjective tools.

This latest research – and earlier studies that have come from the team at DePaul University and from Professor Lenny Jason – is helping to fulfil this need for an accurate assessment tool.

The findings may be used by clinicians to help diagnose ME/CFS and by researchers to design more comprehensive studies.

There is more work to be done, but hopefully DePaul will produce a validated assessment tool in the near future and then begins the task of getting it – and the DePaul Symptom Questionnaire – accepted by the medical profession here in the UK.

This latest research also highlights the importance of researcher collaboration with the ME/CFS community and demonstrates that the community is very willing and eager to help support appropriate research efforts.

The ME Association

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