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Measuring Post-Exertional Malaise with DePaul Symptom Questionnaires: Challenges and Opportunities

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Abstract

Following mental or physical exertion, patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) experience Post-Exertional Malaise (PEM). Although self-report questions represent less expensive and invasive procedures to assess PEM, variability in the wording of the symptom can cause reliability and validity problems. If different PEM measures are used in studies, this could create difficulties in replicating findings, identifying biomarkers, and determining effective treatments for patients. The objective of this article is to describe the challenges and opportunities of the PEM questions of the DePaul Symptom Questionnaires (DSQ) in specific. The five PEM DSQ items can identify 97% of patients with ME/CFS. A brief DSQ-PEM instrument has now been constructed that consists of five DSQ PEM items and five DSQ supplementary items such as symptom duration and how quickly patients would recover from activities. A more comprehensive instrument called the DePaul Post-Exertional Malaise Questionnaire assesses a more comprehensive list of PEM triggers and the duration and length of recovery time from PEM. In this article, we show how the DSQ's PEM self-report items can provide clues to ME/CFS pathophysiology as well as how these items can be used as outcome measures. Future research should focus on contrasting and comparing different ways of eliciting PEM, assessing relationships between PEM self-report questionnaires and biomarkers, and examining the impact of treatment trials on PEM.

Keywords
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; post-exertional malaise; DePaul symptom questionnaire

1. Measuring Post-Exertional Malaise with DePaul Symptom Questionnaires

1.1 Challenges and Opportunities

Following mental or physical exertion, individuals with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) experience a hallmark symptom referred to as Post-Exertional Malaise (PEM), involving a worsening of ME/CFS symptoms [1]. Even the most basic daily activities, including walking, taking a shower, or conversing, might trigger PEM. In severe cases, it can even render a patient bedridden for many days or longer. According to Brown and Jason's [2] meta-analysis, PEM was shown to be 10.4 times more likely to occur among patients with ME/CFS than control participants. These data support the notion that PEM is a cardinal symptom of ME/CFS. There have been over 40 trials using cardiopulmonary exercise tests to evaluate resulting pathological changes, showing amongst others reduced oxygen uptake, increased heart rate, and increased lactate concentration. Abnormalities in the brain and changes in muscle fiber types have also been documented [3-5].

At a physiological level, both sub-maximal and maximal exercise tests have been utilized to evaluate PEM. With the maximal exercise tests, participants are instructed to pedal on a stationary bicycle at a prescribed rate against a gradually increasing resistance until volitional exhaustion or until the participant is unable to pedal at the prescribed rate to measure maximum oxygen consumption or aerobic fitness [6, 7]. Whereas maximal testing requires 5-9 minutes of intense effort, submaximal testing requires a lower level of effort for 25-30 minutes [8]. McManimen and Jason [9] found that PEM scores were more frequent and severe in those with abnormal maximal or submaximal exercise test results than in those with normal findings.

However, according to Meeus et al. [10] and Nijs et al. [11], submaximal exercise tests are not always equivalent to maximal tests. Furthermore, a second testing day of maximal exercise tests needs to be used as patients with ME/CFS only evidence maximal or anaerobic threshold deficits on the second testing day. However, the two-day test can cause a sharp worsening of symptoms for patients with ME/CFS. Because of this, some have recommended utilizing a single test day. However, Keller, Pryor, and Giloteaux [12] found that after completing a single maximal exercise test, 12 out of 22 individuals with ME/CFS were classified as having little to no impairment and 8 as having mild to moderate impairment. This indicates that many patients with ME/CFS have a normal cardiopulmonary response to a one-day physical exercise whereas only a two-day CPET would unmask their impairment.

Furthermore, it is not always possible to conduct maximum and submaximal exercise testing due to the high expenses and specialized equipment required. Noninvasive handgrip tasks [13, 14] are an alternative that Zinn, Zinn, and Jason [15] employed to examine cortical regions showing the part that brain abnormalities play in behavioral symptoms of PEM.

Because of variability in its triggers (type and intensity), symptomology, time of onset, severity, and duration, identifying PEM can be challenging and time-consuming, especially in the context of busy research and clinical settings. Hence, the availability of a low-cost, quick, and accurate screening instrument that can be used “at the bedside” would be valuable. This issue is especially timely given that a substantial percentage of Long COVID patients may also suffer from PEM and the presence of PEM in these patients requires more cautious rehabilitative efforts. Self-report instruments with adequate psychometric properties are an efficient and effective way to assess PEM, but several issues need to be considered when using these types of questionnaires. The objective of this article is to describe the challenges and opportunities of the most widely used self-report measure of PEM, the DePaul Symptom Questionnaires (DSQ).

2. Variability in Self-Report Instruments’ Symptom Wording

While self-report questions offer a less costly and intrusive method of evaluating PEM, variations in the symptom's wording may lead to issues with validity and reliability [16]. For instance, Jason, King, and colleagues [17] found that, depending on how the PEM question was posed, the percentage of patients with ME/CFS who supported PEM ranged from 41 to 94%. The lack of consistency in the way this symptom is measured in PEM self-report surveys is a serious issue since it may lead to the misidentification of some patients as having PEM and the under-identification of others with PEM.

The Fukuda et al. [18] criteria, the commonly used case definition of ME/CFS from the 1990s through the early 2000s, operationalized PEM by asking patients if they were "feeling worse than usual or fatigued for 24 hours or more after exercise." Jason, Evans, So, Scott, and Brown [1] conducted a qualitative study wherein they analyzed replies from individuals with ME/CFS who did not endorse this Fukuda et al. [18] PEM item. Consequently, they were not classified as experiencing PEM using the Fukuda et al. criteria. When closely examining these patients with ME/CFS, Jason et al. [1] found the words “exercise,” “normal daily activity,” “physical or mental exertion,” “physical activity,” “minor activity,” “24 hours or more,” and “daily life activities” connoted important differences regarding whether or not PEM was endorsed. Those patients with ME/CFS who did not endorse the Fukuda et al. [18] PEM question, did indicate that they “experienced high levels of fatigue after normal daily activity.” So, by having a PEM question that was worded more broadly than the Fukuda et al. item, PEM could be identified in these patients who had ME/CFS.

However, if items are too broad, they may identify people who have other distinct other disorders, such as a primary psychiatric condition, as having ME/CFS. Careful wording of items can solve this problem. For example, using a variety of frequency and severity PEM and other symptom items, Hawk, Jason, and Torres-Harding [19] were able to differentiate those with ME/CFS and Major Depressive Disorder with 100% accuracy. So, it is possible to differentiate these important illnesses by using carefully constructed PEM self-report items.

3. DePaul Symptom Questionnaire - PEM Evaluation

Jason et al. [20] found that when healthy controls rated a variety of ME/CFS symptom items, a factor analysis identified only one large unwellness factor, whereas for patients with ME/CFS, several factors emerged including one that measured PEM. Patients with ME/CFS can differentiate their symptom experiences into a variety of PEM and cognitive domains whereas healthy controls

tend to associate these items within an undifferentiated unwellness domain. In 2010, the DePaul Symptom Questionnaire (DSQ) [21] was created using the expanded items from Jason et al.'s [20] survey (See Table S1 for a list of all the DSQ instruments). Its purpose was to evaluate 54 classic ME/CFS symptoms [22] across a range of typologies [23-26]. Each item's frequency and intensity of symptoms were graded using a 5-point rating system. The frequency and intensity of each symptom are multiplied by 25, added together, and divided by 2 to provide a composite frequency/severity score for each symptom that ranges from 0 to 100, with higher scores denoting a greater burden on the individual. Excellent test-retest reliability has been shown for the self-report items [27].

In a factor analytic study of the DSQ [28], a PEM factor emerged, which was able to differentiate patients from controls [29]. A later study by Jason, McManimen, Sunnquist, and Holtzman [30] found that the five PEM DSQ items were able to identify the widest net of patients with ME/CFS (97%), which was higher than any other item from other scales designed to measure PEM. These DSQ items were: 'Dead, heavy feeling after starting to exercise,' 'Next day soreness or fatigue after non-strenuous, everyday activities,' 'Mentally tired after the slightest effort,' 'Minimum exercise makes you physically tired,' and 'Physically drained or sick after mild activity.' These items exhibited good internal reliability, as indicated by an average Cronbach's alpha coefficient of 0.84 [27].

Additionally, people with different chronic health conditions have been distinguished using the DSQ [31]. For instance, Jason et al. [32] found that while some patients with multiple sclerosis do report having PEM symptoms, their frequency and severity ratings are noticeably lower than those of patients with ME/CFS. Furthermore, in another chronic illness group, patients with ME/CFS had much more severe PEM than patients with post-polio syndrome [33].

According to an independent study group's evaluation of the performance of three patient-reported symptom measures in a sample of patients with ME/CFS and matched controls, the DSQ showed the best internal reliability, with less than 5% of patients at the ceiling [34]. Furthermore, the PEM subscale on the DSQ showed great clinical usefulness in that it could distinguish between patients with ME/CFS and controls (a PEM subscale score of 20 optimally distinguished patients from controls). In addition, Slavin et al. [35] have listed the DSQ as a core Common Data Element assessment instrument for ME/CFS.

In 2018, Cotler, Holtzman, Dudun, and Jason [36] constructed a 10-item DePaul Symptom Questionnaire-Post-Exertional Malaise DSQ-PEM instrument consisting of five PEM items from the 54 core DSQ survey plus five supplementary items on the DSQ involving duration of symptom exacerbation after activity, how quickly patients would recover from activities, and evaluating whether participants were not exercising because it made their symptoms worse. The five supplementary DSQ PEM have good internal reliability [27] and effectively categorize patients with ME/CFS versus multiple sclerosis and post-polio syndrome (See Table S2). Using the DSQ-PEM, Jäkel et al. [37] found that PEM correlated in women with an objective marker (lower hand grip strength) and in women and men with higher fatigue ratio. This study provided evidence that both PEM and hand grip strength are sensitive diagnostic tests to assess muscular fatigue and fatigability.

In 2021, with significant patient input, Jason, Holtzman, Sunnquist, and Cotler [38] developed a more thorough PEM tool known as the DePaul Post-Exertional Malaise Questionnaire (DPEMQ) (See Table S3). In addition to asking about popular phrases used to characterize PEM and a list of symptoms that worsen after physical and mental effort, the survey evaluates participants' experiences with PEM. Participants are asked to evaluate a list of symptoms that are exacerbated following physical and/or cognitive exertion and the symptoms included items that had been

assessed through other operationalized measures (e.g., “physical fatigue”, “unrefreshing sleep”, and “flu-like symptoms”), as well as items suggested by patients (e.g., “physical fatigue while mentally wired”, “brain twangs” and “burning sensation all over your skin”). The DPEMQ evaluated the length of PEM's recovery period as well as any potential pacing effects. Pacing was assessed by asking respondents whether pacing allows patients to completely avoid symptom exacerbation, how frequently they find pacing to be effective in avoiding symptom exacerbation, and how effectively they find pacing can reduce the severity of symptoms. Many sensitivities that can trigger PEM (i.e., chemicals, foods, light, heat, cold, noise, visual overload, observing movement, and sensory overload) and positional changes that cause PEM are related to worse physical functioning. Pacing's ability to prevent symptom exacerbations was also strongly correlated with physical functioning.

4. Using DSQ as an Outcome Measure

The scales mentioned above were constructed as a diagnostic scale for determining whether a person met the PEM criteria for a case definition, and thus the period of time being rated was over the past 6 months. These scales along with an abbreviated 14-item brief instrument called the DSQ-SF [39], created in 2019, could be used as outcome measures to chart symptoms over time. This occurred with a study by Oliveira et al. [40] who used this 14-item DSQ-SF. Another set of items for measuring outcomes could be derived from the DPEMQ instrument, which assesses the top 12 symptoms endorsed by at least 80 percent of patients with ME/CFS including reduced stamina and/or functional capacity, cognitive exhaustion, problems thinking, unrefreshing sleep, muscle weakness/instability, physically fatigued while mentally wired, insomnia, aches all over your body, muscle pain, flu-like symptoms, dizziness, and temperature dysregulation. If used as outcome measures, the period of time of 6 months could be reduced to either a month, a week or even at the present time. A pediatric version of the DSQ has already had items changed to the past one month for the pediatric RECOVER study (Personal Communication, Melissa Stockwell, Nov. 2, 2023), as has an adult version of a DSQ for COVID [41]. The DSQ-PEM is also being used as the primary endpoint in a RECOVER-VITAL [42] COVID clinical trial (Personal Communication, David Yanez, Oct. 28, 2023), with the time period being a 1-week look back period. In the RECOVER-ENERGIZE [43] clinical trial, the DSQ-PEM is being used with the following time frames: over the past 3 months, the past 7 days, or since your last visit.

One study examined asking patients with ME/CFS about DSQ symptoms at two assessment intervals (one week apart) and using three distinct recollection time frames (the previous week, the past month, and the last six months) [44]. This study examined if there was a best period of time for assessing ME/CFS symptoms. For memory issues, unrefreshing sleep, and PEM recall, the last month was best, whereas the previous week was found to be excellent for fluctuating joint discomfort. It is probable that important symptoms of this condition are harder to remember on a regular basis when they are perceived as erratic and changeable.

5. Pacing and PEM

It is possible that the PEM self-report items may not identify patients with ME/CFS who are pacing and thus not experiencing PEM. While this issue may occur for briefer periods of time, measuring self-reported PEM over a time period of six months is more likely to capture the majority

of individuals who experience PEM. While it is true some patients minimize PEM due to pacing, most still endorse some experiences of PEM over a six-month timeframe [44].

In the most well-known trial assessing pacing, known as the PACE trial, White et al. [45] found that graded exercise therapy and cognitive behavior therapy were more effective than pacing in conjunction with specialized medical care. However, pacing and learning to stay within one's energy boundaries are tactics that patients overwhelmingly support and report as the most helpful ways to cope with PEM and ME/CFS [46, 47]. Therefore, it was unexpected and puzzling to learn that the pacing intervention used in the PACE trial was no more beneficial than specialized medical treatment.

The PACE trial's efficacy might have been affected by the way pacing was handled [48]. More precisely, the researchers PACE intervention advised patients to avoid exceeding 70% of their perceived energy limit, to decrease the incidence of PEM. Patients may, however, become overly sedentary if their energy expenditure is continuously less than their energy availability. Put differently, this pacing technique instructed patients to do less than what their energy level would have permitted. This technique may have unintentionally increased social isolation by taking less action than patients have the ability to undertake [49].

On the other hand, the mid-1990s saw the development of the Energy Envelope Theory, a method of pacing that contends that there needs to be a balance between perceived and expended energy [50, 51]. Stated differently, an individual has an energy battery, and if their battery is at 70% of what it had been prior to ME/CFS onset, the person can use up to 70% of that battery [47]. In other words, patients can use or engage in activities up to their perceived or accessible energy. This method uses the term "staying within the envelope" to describe an acceptable range of energy use, in which an individual avoids both overexertion and under-exertion, maintaining an optimal level of activity over time and which theoretically might reduce the occurrences of PEM.

Planning activities and adhering to the Energy Envelope are examples of pacing interventions. Activity planning may help people with ME/CFS control excessive energy expenditure and avoid PEM. It is consistent with the self-regulatory behavior change strategy known as "Action Planning" [52]. Several studies have shown that patients with ME/CFS who stay inside the Energy Envelope have lower PEM severity, better physical functioning, lower ME/CFS symptom scores, and more hours spent active per week than those who have less energy available [53-55]. For example, in a treatment trial involving more than 100 patients, patients who received one of several non-pharmacological therapies were split into two groups: those who were effective in keeping their energy used close to their available energy versus those who were not able to stay within their energy envelope. Physical functioning and the degree of fatigue improved significantly in individuals who were able to stay within their energy envelopes as opposed to those who did not [56]. These results imply that assisting patients with ME/CFS in maintaining optimal energy expenditures in accordance with their available energy reserves can help lower fatigue and enhance functioning over time.

Wold et al. [57] found that patients could be categorized into three groups based on the results of a variety of DSQ instruments: patients with fatigue, patients with PEM, and patients with multi-dimensional PEM (experiencing exertional malaise after both physical and mental/social efforts above their threshold requiring a long recovery period). While activity-based treatment generally resulted in an increase in reported symptom severity, pacing within the patients' activity threshold was found to improve or minimize the severity of the symptoms. Kielland, Liu, and Jason [58] found

that the DSQ PEM score was a reliable indicator and suitable instrument for determining patients with ME/CFS tolerance for different treatment interventions.

Pacing is generally helpful for people with ME/CFS, according to Sanal-Hayes et al.'s [59] scoping review of 17 articles on the topic. According to their findings, activity planning, consistency, and energy management tactics that lower PEM were good pacing strategies. Activities and other behaviors (sleep, food, stress) could be associated with episodes of PEM through the use of longitudinal activity tracking and contemporaneous heart-rate feedback. Unfortunately, only two studies used PEM as an outcome measure, and the majority of studies neglected to evaluate the various and important ME/CFS symptoms. The studies frequently did not include participant characteristics, which restricts the conclusions that may be made about the patient population. Furthermore, there were few randomized control trials, small sample sizes, uncertain power to detect change, and poor to fair methodological quality in the investigations. Better controlled studies are needed.

Many patients have turned to heart rate monitoring in an attempt to pace, with encouraging self-reports [60]. Finally, the Recover Energizer is currently implementing a 3-month trial of structured pacing with a coach or PEM education for those with Long COVID (https://trials.recovercovid.org/). The results of this trial will be of interest for the scientific community.

6. Long COVID and PEM

Twomey et al.'s [61] survey of 213 adults with Long COVID found that 95% met the threshold for at least one of the 5 core PEM DSQ items, and 59% met even stricter criteria (saying yes to items 7 and 8 and having symptoms lasting for at least 14 hours). Comparable results were found by another sample of 465 patients with Long COVID [62]. Recently, Ejalonibu et al. [63] recommended the use of the DSQ-PEM in a review of patient-reported outcome measurement instruments that can be used to comprehensively characterize Long COVID.

Hua, Schwabe, Jason, Furst, and Raicu [64] used random forest algorithm-based models with a long COVID sample to predict whether or not participants would meet the criteria for ME/CFS roughly six months after COVID-19 infection. With an accuracy of 95%, early symptoms, especially those measuring PEM, predicted the onset of ME/CFS. Next, the authors examined the best eight symptoms that could reliably predict ME/CFS, five of which were associated with PEM. The accuracy of the feature-reduced models was 94%. The results showed that a number of ME/CFS symptoms including PEM that appeared in the first few weeks following COVID-19 infection predicted Long COVID and the diagnosis of ME/CFS after 6 months.

Using a 14-item short form of the DSQ, Oliveira et al. [40] found considerable similarities between patients with Long COVID and ME/CFS at baseline, including high rates of PEM. For the Long COVID patients, symptoms improved over a year but not for the patients with ME/CFS. Also using the DSQ-SF, McGarrigle et al. [65] that found "Cold limbs" and "Flu-like symptoms" were only occasionally found in Long COVID whereas they are more often reported in ME/CFS, so these symptoms were found to be the best items to differentiate these two diseases.

In a study by Gattoni, Asghar, Ferguson, Carrie, et al. [66], using the modified DSQ, no significant differences between day-1 and day-2 maximal exercise tests were found. However, other investigators with Long COVID samples have found pathological findings following cardiopulmonary

exercise tests in long-COVID [67]. For example, Appelman, Charlton, Goulding, et al. [5] found severe muscle damage, a disturbed immune response, and a buildup of microclots following the exercise tests.

7. PEM Self-Report Items Can Provide Clues to Pathophysiology

It is important to distinguish between tachypnea, which is merely abnormally rapid breathing that is typically found in asthma and lung infections, and hyperventilation, which is characterized by both an excessive breathing rate and depth of ventilation leading to the loss of carbon dioxide and commonly associated with anxiety disorders. In a study by Cotler, Katz, Reurts-Post, Vermeulen, and Jason [68], using cardiopulmonary exercise testing, individuals with ME/CFS had their resting respiratory rates recorded on two separate days. A substantial predictor of abnormally rapid breathing was the DSQ-PEM but not sedentary behaviors and psychological/somatic tests. According to these findings, PEM was considered a physical symptom of ME/CFS which is caused by underlying physiological dysfunction rather than psychological issues.

Nepotchatykh et al. [69] found differential circulating miRNA expression signatures between ME/CFS, FM, and ME/CFS plus FM, which also correlated to symptom severity between ME/CFS and ME/CFS plus FM groups. Among those with ME/CFS, miR-150-5p expression correlated positively with DSQ PEM scores, but among those with ME/CFS plus FM individuals, miR-150-5p negatively correlated with DSQ PEM scores. These results and others of this study demonstrate that ME/CFS and ME/CFS plus FM are two distinct illnesses.

8. Discussion

There are numerous challenges with using self-report questionnaires to measure PEM. We have found that our DSQs that measure PEM items can be used as a screening tool to see if a person fits the diagnostic criteria for ME/CFS. To rule out any potential exclusionary medical illnesses, it is crucial to follow up initial screening of self-report symptoms with a thorough medical evaluation. Such a strategy occurred with Strand et al. [70], who found that the DSQ identified 60 individuals with ME/CFS whereas the physicians identified 56.

Some research has also suggested that there might be different types of PEM. With a sample of over 700 patients, McManimen, Sunnquist, and Jason [71] found that PEM items can be differentiated into Muscle and General PEM factors. Ninety-five percent of patients indicated having at least one symptom in the General factor (related to a generalized feeling of physical or mental fatigue following exertion) whereas 99% of patients indicated having at least one PEM item on the Muscle factor, which was composed of five symptoms that referred to pain, weakness, or fatigue in muscles following exertion. In addition, McManimen and Jason [72] found that those patients with ME/CFS with a comorbid diagnosis of FM displayed significantly more frequent and severe PEM symptoms in the Muscle and General PEM factors than those without comorbid FM. In a recent meta-analysis, Barhorst et al. [73] found people with ME/CFS and FM experience small to moderate increases in pain severity after exercise.

The assessment of PEM can also be used as a tool in patients with autoimmune diseases (e.g., ANCA-vasculitis) complicated by ME/CFS [74]. However, any screening device can misclassify people who do not experience PEM as being affected by it. Many chronically ill patients in medicine experience post-exertional symptoms. For example, patients with arthritis experience pain; those

with asthma experience shortness of breath; and others with coronary artery disease, experience chest pain. However, patients with ME/CFS experience unusual symptoms after exertion that other patients and healthy people might not. For example, worsened sleep, the appearance of flu-like symptoms, and a noticeable decline in function due to symptoms. If patients are erroneously categorized as being affected by PEM, that could lead to inappropriate inflation on the population level and misdiagnoses on the individual level of ME/CFS. Using the DSQ-PEM or its variations in populations with known post-exertional symptoms beyond fatigue but without the cardiopulmonary exercise test abnormalities seen in people with ME/CFS could yield interesting insights.

Since the development of the DSQ, several new ME/CFS case definitions have emerged such as the IOM [75] and the ME-ICC [76]. Fortunately, the DSQ can determine whether individuals might meet criteria for these later criteria [77]. Our research group recently developed a revised instrument called the DSQ-2 [78] to include new items, some based on Ramsay's [79] criteria (Prolonged worsening of symptoms after physical activity, Muscle fatigability after minor exertion, and muscle weakness after minor exertion), and also the ME-ICC (symptoms worsen with exertion, [76]).

Many other events can cause PEM (such as exposure to environmental stress or mold), and there can be many other types of PEM consequences such as severe flu-like symptoms, which is the reason we have developed the DPEMQ, which is a more comprehensive instrument to assess PEM. When PEM is measured in the laboratory, with a challenge involving exercise or motor activity in maximum cardiopulmonary tests, these tests only measure exertion of a physical type, but self-report questionnaires can tap other activities that can cause exertion in more naturalistic settings [38, 80].

In the last few years, there has been more interest in measuring PEM. For example, Mateo et al. [81] used open-ended questionnaires following two maximal exercise tests, at five time points, and found the symptoms with the greatest frequency were fatigue, cognitive dysfunction, and sleep problems. In another study with ME/CFS, after a cardiopulmonary exercise test, Stussman et al. [82] found that semi-structured qualitative interviews were able to capture changes in PEM severity and symptom quality, whereas visual analog scales failed to do so. Davenport et al. [80] recently developed the PEM/PESE Activity Questionnaire to measure activities of daily living, and this scale had generally fair to excellent test-retest reliability. Sivan et al.'s [83] modified COVID-19 Yorkshire Rehabilitation Scale evaluates the role of all types of exertion (physical, cognitive, and emotional) on PEM and the type of symptoms that constitute PEM for patients with Long COVID [84]. Finally, the recently published FUNCAP [85] evaluates functional capacity considering PEM consequences.

Our DSQ PEM items have demonstrated strong psychometric properties (e.g., test-retest reliability, construct validity, predictive validity, sensitivity/specificity, discriminant validity, etc.). The DSQ has been translated into multiple languages and is currently being used in the US, Canada, Mexico, Asia (e.g., Japan), Australia, New Zealand, the Middle East (e.g., Iraq), Europe (e.g., Great Britain, Ireland, Spain, Portugal, Germany, France, Poland, Belgium, Netherlands, Luxembourg, Finland, Denmark, Latvia, Norway, Sweden), and South Africa. In a study involving 40 countries, the DSQ-PEM has been translated so that it can be used for immigrant language groups in the following countries: Argentina, Australia, Austria, Brazil, Bulgaria, French, Spanish, Croatia, Ecuador, Egypt, Finland, Georgian, Germany, Greece, Hungary, Hebrew, Israel, Italian, Japanese, Malaysia, Mexico, New Zealand, Peru, Philippines, Poland, Romania, Serbia, Singapore, Spain, Switzerland, Taiwan,

Thailand, Ukraine, and Vietnam (Personal Communication, Natalie Quintero, Nov. 27, 2024). In addition, our DSQ PEM instruments have been used in a variety of investigations [14, 42, 61, 86-94]. In addition, the DSQ has recently been used in a COVID study of two thousand four hundred forty-five individuals with COVID primarily from Egypt, India, Pakistan, Syria, and Yemen [95].

There are multiple questions that need to be more thoroughly investigated in future PEM research. Self-report questionnaires and diaries might not fully capture the complexity of PEM, especially for patients who have reduced their activities to avoid or reduce PEM symptoms. Questionnaires could include items that evaluate things like what would happen if a patient participated in activities that would require exertion and whether they are pacing to lessen symptom flare. We need a better understanding of the limitations of the various assessments in terms of the range of symptoms they cover and their capacity to identify PEM triggered by stimuli other than physical exercise. Triggers can be assessed by words like “slightest,” “minimal,” or “every day” to imply low-intensity triggers, but this should be further explored, as well as phrases like “unanticipated” or “out-of-proportion” to illustrate the relationship between triggers and PEM symptoms. More work is needed on the capability of the instruments to differentiate between PEM, cardiopulmonary problems, and deconditioning. In addition, future validity studies need to consider both the criteria regarding symptoms (e.g. fatigue, exhaustion, “feeling like dead”, etc.) and what kind of triggers are relevant (e.g. are specific activities needed to elicit PEM).

Future research should focus on contrasting and comparing different ways of eliciting PEM, assessing relationships between PEM self-report questionnaires and biomarkers, and examining the impact of treatment trials on PEM [96]. More research is needed to differentiate between the experience of PEM and the underlying biological responses of PEM. Although the literature provides some support for an association between biological responses and self-reported PEM, we need more information about the nature of this association and the mechanisms behind it [97]. Appropriate measurement of PEM can lead to more success in reproducing results among various laboratories, identifying biomarkers, and ascertaining whether treatments are beneficial to patients [98].

Author Contributions

The author did all the research work for this study.

Competing Interests

The author has declared that no competing interests exist.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Table S1: DePaul Symptom Questionnaires.
2. Table S2: DSQ-PEM.
3. Table S3: The DePaul Post-Exertional Malaise Questionnaire (DPEMQ).

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