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Approaching recovery from myalgic encephalomyelitis and chronic fatigue syndrome: Challenges to consider in research and practice

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Abstract

There are unique methodological challenges to studying and assessing recovery in myalgic encephalomyelitis and chronic fatigue syndrome. This study explored these challenges through interviewing 13 physicians who treat myalgic encephalomyelitis and chronic fatigue syndrome. Our deductive thematic analysis produced four themes to consider when approaching recovery: lifespan differences in the illness experience; the heterogeneity of myalgic encephalomyelitis and chronic fatigue syndrome—case definitions, etiological stance, and misdiagnosis; patient follow-up and selection bias; and assessment logistics. We discuss how researchers and clinicians can use these considerations when working with patients, drafting recovery criteria, and interpreting treatment outcomes.

Keywords

assessment; chronic fatigue syndrome; illness experience; myalgic encephalomyelitis; myalgic encephalomyelitis/chronic fatigue syndrome; physician; qualitative methods; recovery

Recovery from myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS) is a relatively understudied area. With no operationalized definition, and no consensus of how to measure recovery, the field's understanding of recovery is limited (Adamowicz et al., 2014). The most recent review of ME and CFS recovery rates without treatment was by Cairns and Hotopf (2005), who found a median recovery rate of 5 percent (range: 0%–31%). However, Cairns and Hotopf's (2005) findings were limited by the reviewed studies' heterogeneity of samples and varied research methods. A study's inclusion criteria, for instance, can significantly affect the proportion of patients that are reported to recover (Nacul et al., 2017). Such considerations should be made more apparent to improve future research.

In recent years, the Pacing, graded Activity, and Cognitive behavior therapy; a randomized Evaluation (PACE) trial has brought attention to this issue (White et al., 2013). The PACE

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trial, to date, was the largest treatment trial for CFS that compared the effectiveness of specialist medical care (the control condition) to adaptive pacing therapy, cognitive behavior therapy (CBT), and graded exercise therapy (GET). Originally, White et al. (2013) purported that 22 percent of patients with CFS recovered after CBT and 22 percent recovered after GET. However, patients, researchers, and physicians have voiced their criticisms over the PACE trial (Geraghty, 2016; Nacul et al., 2017).

One core methodological concern was the purportedly loose recovery criteria used by PACE (White et al., 2013). As Geraghty (2016) mentions, some trial participants could have fulfilled criteria for recovery before entering the trial. Under the more stringent recovery criteria from the original protocol, a reanalysis of patient outcomes found recovery rates of just 7 and 4 percent, respectively, for CBT and GET (Wilshire et al., 2017). These disparate results highlighted a challenge to studying recovery—there is no consensus for defining and measuring recovery from ME and CFS (Adamowicz et al., 2014).

Working toward a consensus, our research group conducted two qualitative studies investigating how patients and physicians conceptualized recovery from ME and CFS (Devendorf, Jackson, Sunnquist et al., 2017; under review). Our findings highlight the need to differentiate recovery from significant improvement, as previous studies have used terms such as “partial recovery” and “full recovery,” which can be misleading (Knoop et al., 2007). These interviews also revealed the complexities of recovery. Both patients and physicians felt recovery should be defined and measured using many domains, including daily functioning, symptomatology, quality of life, and physical functioning. These domains should be considered in research and practice.

The next steps toward operationalizing recovery are quantifying these domains and agreeing on specific measures. Pursuing this endeavor, it is important to note the unique difficulties to studying recovery. ME and CFS are chronic, multi-system illnesses that are diagnosed by case definition. These aspects complicate how physicians conceptualize, diagnose, and treat ME and CFS (Åsbring and Närvänen, 2003). This study’s goal was to explore physicians’ views on the challenges to studying and approaching recovery. Our aim was to examine these challenges in-depth and provide recommendations that will improve how researchers and practitioners approach the study and quantification of ME and CFS recovery. We explored the views of physicians who treat ME and CFS to investigate this question. With their experiences treating patients, physicians can provide a nuanced account of ME and CFS recovery from a research and clinical perspective.

Methods

Design

We used a qualitative approach, conducting semi-structured interviews with physicians and analyzing the data using deductive thematic analysis (Braun and Clarke, 2006).

Participants

We recruited a non-probabilistic, purposive sample of 10 physicians who specialize in ME and CFS (Guest et al., 2006) and assessed for saturation. Our sample size was informed by

Guest et al. (2006), who recommend that interview structure (e.g. open versus structured), research aims, and homogeneity influence sample decisions. Previous ME and CFS qualitative studies have utilized similar sample sizes (e.g. Åsbring and Närvänen, 2003, N = 12 CFS physicians). Specialists were defined by their extensive patient experience, research contributions, and significant involvement in the field (e.g. running ME and CFS specialty clinics, participating on committees). L.A.J., an ME and CFS expert, provided recommendations for contacting 17 physician specialists. In all, 10 of these specialists responded and participated.

Due to a lack of medical specialists in the field, we asked our participants for referrals to other physicians who had experience treating patients with ME and CFS. This led our team to interview three other physicians who did not identify as ME or CFS specialists. One physician was a pediatrician; two were psychiatrists. While coding for "What are the challenges associated with studying recovery from ME and CFS?" we felt that these non-specialists extended on the coded data from the specialists, which provided us a richer analysis of these nuanced challenges. We assessed our results for saturation throughout the data collection process. We determined that we reached saturation when there was enough information to replicate the study and that no new themes emerged with more interviews (Fusch and Ness, 2015). DePaul University's Institutional Review Board provided ethics approval to conduct this research.

Our sample's mean age was 60 years old, with nine males and four females. For years in practice, three physicians had 30 or more years, seven had 20–29 years, one had 10–19 years, and two had 1–9 years of medical experience. Our sample was diverse in their medical specialties: epidemiology (n = 1), geriatrics (n = 1), infectious diseases (n = 1), neurology (n = 1), internal medicine (n = 2), psychiatry (n = 2), general medicine (n = 3), and pediatrics (n = 5). It is important to note that three physicians identified with two medical specialties.

Procedures

A.R.D. conducted phone-based, semi-structured interviews with participants. All participants provided informed, verbal consent before being interviewed. One participant completed the interview via email and provided written consent. The email interview was comparable to the phone interviews in terms of content, length, and effort. There was no evidence that the email format inhibited the participant from candidness. Our interviews asked physicians about their general thoughts on recovery from ME and CFS—defining, measuring, and studying recovery. These questions were inspired by online, patient discussion boards discussing the PACE trial, and they were generated based on discussions with an expert in the field (L.A.J.). A.R.D. asked follow-up questions to expound upon participants' responses. Interviews were audio-recorded (M = 31 minutes), transcribed verbatim, and verified for accuracy.

Data analysis

We followed the same procedure as our first report (Devendorf et al., 2017). Because we coded for specific research questions pertaining to recovery, we utilized a deductive thematic

analysis to explore challenges to studying recovery from ME and CFS. Our realist approach was fitting with our goal to "provide a more detailed and nuanced account" of methodological challenges (Braun and Clarke, 2006: 11). A.R.D. and C.T.J. coded the interviews. A.R.D. was a research assistant who has studied ME and CFS for 4 years. C.T.J., a research intern, became acquainted to the field before coding through immersing in literature on recovery, qualitative methods, and controversies in the field (e.g. case definitions). Analysis proceeded in six stages.

In stage 1, coders searched for meanings and patterns by reading and rereading participants' transcripts, while revisiting audio recordings. Codebooks were developed after each researcher coded three unique interviews. In stage 2, coders developed a final codebook with guidelines, definitions, and examples of codes. This process occurred after each researcher coded the same manuscript and met to assess line-by-line congruence (Campbell et al., 2013). Inter-rater reliability was established for 20 percent of the interviews ($n = 3$). Our overall inter-rater reliability was good after weighting each code on all three interviews ($K = .85$; McHugh, 2012). We coded the remaining 10 transcripts, each researcher coding five transcripts.

Stage 3 consisted of organizing and summarizing our emerging themes. Visual representations such as mind maps, charts, and written notes augmented this process, allowing us to see relationships between themes. In stage 4, we revised our themes until they were distinct and coherent. This required us to collapse and combine some initial themes. We defined, finalized, and named our themes in stage 5. M.S. and L.A.J. ensured our analysis was credible (Elliott et al., 1999). In stage 6, we picked representative quotes to illustrate findings.

Results

Four themes emerged as challenges for physicians to either assess or study recovery: (1) lifespan differences in the illness experience; (2) the heterogeneity of ME and CFS—case definitions, etiological stance, and misdiagno-sis; (3) patient follow-up and selection bias; and (4) assessment logistics. We present these challenges in detail and provide our sample's recommendations for approaching them. See Table 1 for additional descriptive quotes.

Theme 1: lifespan differences in the illness experience

This theme highlights the need to consider the age of patients when studying recovery from ME and CFS. Physicians noted that ME and CFS may present differently in children than adults. However, there is little, if any, research that demarcates these differences. For instance, some studies suggest that younger individuals experience better prognostic outcomes:

> There are very few studies that compare uhh, adults-onset-patients with pediatric-onset-patients, in terms of, you know, those are often not included in the same study. And so, yeah, we think that adolescents tend to do better. But, we don't have great data on that. (P4)

The meaning of patients' symptoms—how symptoms affect their daily life—also evolves with age, which researchers should consider when comparing functional outcomes between younger and older samples. Experiencing pain in the shower, for instance, may be more dangerous for an older individual than an adolescent. Different age groups also have different goals, responsibilities, and obligations. Children attend school, participate in extracurricular activities (e.g. sports), and regularly interact with their peers. Younger adults might be in college, a first job, or feel pressured to be romantically involved. Middle-aged adults might be caregivers, for children or older family. Older adults may experience more isolation and have diminished physical abilities:

> I mean, you tell the truth, the older you get, the more tired you get; that's just life. If you ask me, I think I used to have better energy when I was younger for sure. Is that because I have CFS? No, that's because I'm no longer 25. (P13)

Cognitive abilities and self-awareness also develop with age. Younger children may lack awareness that they are sick, or the ability to articulate their experience. Symptoms such as fatigue, orthostatic intolerance, and memory issues may be difficult to detect in pediatric populations. Symptom screenings should be sensitive to these developmental confounds:

> [M]any times one of the problems with the way we ask questions is we don't, the kids can't know how much, for example, orthostatic intolerance is really affecting them. So when we ask them, 'How much of an impact does this have on you?' They can't separate out how much pain impact that has versus the pain from their headaches versus the insomnia. (P4)

To address these issues, studies could include caregivers' perceptions of their children's health for younger age-groups. When dealing with larger datasets with an array of age groups, physicians recommended using age-matched controls to account for the physical, cognitive, and goal-oriented differences that accompany age.

Theme 2: the heterogeneity of ME and CFS—case definitions, etiological stance, and misdiagnosis

For years, the heterogeneity of patients in the ME and CFS field has troubled researchers and clinicians. With no consensus on inclusion criteria, research has been inconsistent in reporting patient outcomes. This problem extends to studying recovery—both predicting recovery and determining recovery. Case definitions affect whether a patient is diagnosed with ME or CFS, and may select more or less severe cases. Physicians alluded to this issue in their practice. Compared to other chronic illnesses, this sample felt there is more variability with ME and CFS patients, which requires more individualized treatment goals. With the widely used Fukuda et al. criteria (1994), for instance, it is possible for two patients to have a diagnosis of CFS without having any of the same symptoms (except for fatigue). This issue confused some physicians to the point where a few questioned their patient's symptoms:

> It's probably not one disease. It's a fairly nonspecific thing, so it's probably different things. There's probably one real CFS, and there's a bunch of pretenders, I don't know. I think it's very poorly described and delineated. (P13)

Many experts screened patients for exclusionary diagnoses, like anemia. A few mentioned "landing" on a ME or CFS as a diagnosis when no cause was discovered:

> I know it's a diagnosis of exclusion. So you have to exclude all these other disorders before we can kind of settle on them as a diagnosis. That's why it's diagnostically difficult. It has a lot of vague symptoms. (P12)

Depending on the case definition used by the physician, patients may be diagnosed differently between providers, which could delay appropriate treatment for patients. As a result, physicians see a spectrum of ill individuals with an array of symptoms. Physicians noted this issue affects clinicians' and researchers' recovery views, as illness severity may influence an individual's prognosis. Some physicians believed that more severe individuals were less likely to recover:

> [Y]ou have to understand that I see an extremely skewed patient population. These are individuals who found me after they've been suffering from this illness, and then seen multiple doctors. So, the patients I see tend to be on the sickest end of the spectrum, and they have, uh, not got much better. (P11)

Etiological views also varied among this sample. Most believed ME and CFS were physiologically based (Participant 7 believed in ME but not CFS); two believed ME and CFS were temporary diagnoses; and two physicians (both psychiatrists) believed they were psychiatric illnesses that were depression variants. As mentioned in the methods, we still included these psychiatrists because they contributed to illustrating the challenges faced by the ME and CFS field. Importantly, these varying etiological stances affected how physicians treated patients and viewed recovery from these illnesses:

> And what I usually do on the first visit, I say, okay, in this person's situation, 80% of the complaints are organically-based. And, 20% are poor coping, poor adaptation, depression, anxiety, whatever you want to call it. (P1)

This challenge highlights two needs for researchers and practitioners. The first is echoed in the literature—there needs to be a consensus on clinical and research case definitions.

The second need is to understand the relationships of ME and CFS to depression to avoid skewing recovery rates. Regardless of their etiological views, this sample acknowledged that the patients they see often exhibit depressive symptoms, perhaps because of the isolation, confusion, uncertainty, and life changes (e.g. physical capabilities) that accompany ME and CFS. Concurrently, physicians mentioned that misdiagnosis occurs on both ends. Patients may be misdiagnosed with depression, when they really have ME or CFS. Diagnosing patients with depression—when they really have ME and CFS—may have detrimental effects, as this process is inherently stigmatizing, delegitimizing, and damaging to patients because they may inadvertently seek inappropriate care:

> [Other] doctors say, 'Oh. You've got chronic fatigue syndrome. Therefore, he's psychotic or depressed or delusional, or something.' And they never look again, and they fill them up full of anti-psychotics that cause them to have liver damage, causes them to have brain damage from the uhh, anti-psychotics in some cases. (P7)

Conversely, patients may be misdiagnosed with ME and CFS when they really have depression. This misdiagnosis could skew recovery rates for ME and CFS, as recovery from depression is more common than ME and CFS, especially when studying CBTs.

Theme 3: patient follow-up and selection bias

This theme identifies challenges in measuring patients' progress over time in research and practice. There is currently a dearth of longitudinal research for both the natural course of ME and CFS and post-treatment outcomes. This sample echoed these concerns and noted that tracking patients in their practice is a considerable challenge. Ideally, physicians would stop seeing patients because a treatment works or patients feel better. While this may be the case, physicians acknowledged that there is often uncertainty for why patients stop making appointments. For instance, patients may be unable to afford treatment, lack time to make an appointment, or seek treatment elsewhere. One specialist emphasized the high treatment costs:

> You know, I've seen lots of people who go to these fancy clinics, spend $8,000 for the first visit, and they come back and I say, 'Are you cured?' And they say, 'No. I'm not really feeling anybody different.' 'Well, so and so said you were cured.' And that's one of the big problems. (P1)

However, some patients do stop making appointments because they improve. If patients have recovered, they are less likely to participate in research; in this scenario, practitioners and researchers may underestimate improvement and recovery rates. Symptoms of ME and CFS fluctuate day-to-day in severity, which reemphasizes the need to track patients. More research on the course and daily challenges of ME and CFS could illuminate the nuances of measuring improvement:

> When someone gets cancer … there are some unknowns, but we are able to prognosticate it, use data to estimate prognosis for people so they have some idea for what to prepare for, and how to tackle the next increment. And we don't have very much of that for our patients. (P5)

Some physicians followed up with their patients over phone or email. This communication benefits both the physician and patient. Physicians gain feedback about their practice through talking with the patient, while learning more about the course of ME and CFS. Meanwhile, patients feel supported by their doctor, save money, and avoid the risk of a symptom flare:

> I mean, it'd be great to have a mostly disciplinary team approach … But with chronic fatigue, that's really hard because getting the energy to get out of the house and to do all of the stuff you need to do is really tough. (P2)

Physicians also recognized that medical research is confounded by an inherent sampling bias —enrolling individuals who are sick. Many noted that the individuals who recover from ME and CFS tend to do it in the early stages of the illness. These individuals then leave the ME and CFS community and are excluded in research samples:

> I think we don't have very good longitudinal data. And, there's a strong selection bias in every, all of our observations in studies for the people that remain sick.

> Because when people get better, we don't track them very well—especially the people that get better early … So, I think we probably underestimate the number of people who get better early in the disease. (P5)

To address this challenge, research should use "large, community-based, longitudinal studies where patients are diagnosed accurately and assessed with good outcome measures to assess the true recovery rates" (P6). Using prospective designs would also allow researchers to examine prognostic predictors such as age, illness onset, illness duration, severity, and biomarkers of ME and CFS. However, physicians noted these designs are expensive, and funding for ME and CFS research is notably lower compared to other illnesses (Dimmock et al., 2016). Physicians expressed these funding issues extend to randomized treatment trials, which are currently underpowered by relatively small samples:

> [Regarding drug trials for Rituximab] This has been 5 years, and, have there been any studies in this country to try and reproduce this? No. And this is a drug that's already approved—that's what annoys me, is that this should be studied like crazy. (P1)

Inherently, recovery from ME and CFS has been understudied because there is a lack of opportunity to study the topic. Until there is more funding allocated to ME and CFS, tracking convenience samples recruited from medical clinics may provide more information on the course of this illness. But to obtain more accurate recovery rates, researchers should track large, community-based samples over time.

Theme 4: assessment logistics

This final theme elucidates challenges in measuring recovery. As presented in the first analysis of this data (Devendorf et al., 2017), this sample viewed recovery as multidimensional, recommending that researchers consider patients' symptomatology, daily functioning (e.g. running errands), physical functioning (e.g. exercise), occupational functioning, and quality of life. Ideally, these domains would be captured with a combination of self-report and objective data and a full medical evaluation in research. However, administering the many questionnaires that target these recovery domains would be time-intensive and expensive for research and practice. Physicians already spend time screening patients:

> I do a history, which, for me, takes a minimal of two hours. And, do a family history, which takes a minimal of 1 hour. So we're at 3 hours. (P7)

These practical barriers should be transparent in research, as well as how they limit the scope of treatment outcomes:

> For improvement, some justification can be made for measuring less but then that should be made clear. For example, if a medicine is intended to treat only post-exertional malaise, then it is not unreasonable to only measure items related to post-exertional malaise in a study of that medicine. (P6)

With ME and CFS particularly, physicians said recovery is tricky to assess because patients cope with it differently. Lifestyle factors such as diet, sleep hygiene, and pacing could affect patients' presentations of their illness. Such variables can mask a patient's disability:

> So, I see some people who have very severe illness, but they cope with it fantastically—you'd never even know they were sick. (P1)

While effective coping is encouraged, physicians conceptualized recovery as the complete remission of ME and CFS symptoms, without the need to cope or adjust one's daily life. Physicians recommended screening for coping strategies, while being patient, observant, and confidant to discern between symptom management and true improvement. Objective measures could also, to some extent, control for coping. Physicians mentioned the use of neuropsychological testing, actigraphy, and heart rate monitors.

Discussion

This study examined physician views on studying and assessing recovery from ME and CFS. Our goal was to illuminate these unique challenges to improve the reporting of recovery in research and practice. Physicians and researchers have acknowledged that recovery is multidimensional and subjective. In response, objective measures such as actigraphy, cardiopulmonary exercise testing, and the National Aeronautics and Space Administration (NASA) 10 Minute Lean Test have been proposed (Devendorf et al., 2017). However, self-report measures, like the 36-Item Short Form Survey (SF-36; Ware and Sherbourne, 1992), continue to be the primary assessment for improvement (e.g. Janse et al., 2017; White et al., 2013). Our findings provide considerations for researchers and physicians when using these instruments.

One consideration for measuring recovery is age. Like other chronic illnesses that are diagnosed by case definition (e.g. fibromyalgia), ME and CFS may present differently in children than in adults. Our findings align with proposed pediatric case definitions (Jason et al., 2006; Rowe et al., 2017), which highlight the differences in approaching ME and CFS in children. For instance, children may experience rashes and abdominal pain, but these symptoms may not be common in adults. Researchers and physicians should also be sensitive to patients' developmental capacities (e.g. cognitive development, expressive language abilities for symptom descriptions), contextual variables (e.g. school vs work), and goals (e.g. playing school sports vs taking a vacation). Parent and teacher consultation could be beneficial when evaluating children younger than 10 years (Rowe et al., 2017).

However, our findings demonstrate these differences extend beyond comparing pediatric and adult samples. The experience of ME and CFS could vary between children, adolescents, emerging adults, middle-aged adults, and older adults because the meaning of ME and CFS symptoms changes over time. A symptom like pain, for example, carries a different meaning for older adults, living alone, than middle-aged adults living with a family. Screening for patients' access to resources (e.g. caregivers, medications) could provide helpful information. Many studies utilize the SF-36 physical functioning domain (Ware and Sherbourne, 1992) to assess improvement in adults and the Child Health Questionnaire for children (Landgraf et al., 1996). These instruments have participants report how their health status affects items such as "climbing several flights of stairs," "bending kneeling, or stooping," and "bathing and dressing." While these items are efficient methods to capture aspects of daily life, we recommend that researchers also include open-ended self-reports to

supplement these standardized measures. Open-ended questions would allow participants to detail their experiences. Although these supplements would be subjective and time-consuming to code, previous work has shown that physicians and patients, alike, feel recovery should be appraised by the patient (Devendorf et al., 2017, undergoing revisions). Researchers should also compare their samples to culture-specific, age-matched norms when considering these scales. The SF-36, for instance, provides mean scores by age cohort, allowing for researchers to estimate the level of expected functioning at a given age (Ware and Sherbourne, 1992).

In addition to age, our sample identified the heterogeneity of ME and CFS as a challenge to studying recovery. This challenge has been observed throughout the history of the field, and has made it difficult to predict the natural course of ME and CFS (Cairns and Hotopf, 2005) or accurately assess post-treatment outcomes (White et al., 2013). Our sample noted that, compared to treating other chronic illnesses, there is considerable diversity in the severity of patients with ME and CFS. Physicians remarked that ME and CFS are characterized by vague and poorly delineated symptoms, such as fatigue or concentration issues. This ambiguity led to problems in diagnosing patients, sometimes mistaking them for having depression. This challenge has considerable implications for measuring recovery, as recovery from depression is more common. One study found 50 percent of depressed individuals with a first-onset episode recover from depression and have no future episodes (Eaton et al., 2008).

These findings suggest that practitioners should attend closely to the differential diagnosis between ME and CFS and psychiatric disorders (Griffith and Zarrouf, 2008). This sample expressed the potential harm that follows when a patient is misdiagnosed. Patients who have ME and CFS, but are misdiagnosed with depression, may feel stigmatized, delegitimized, and may be prescribed potentially harmful treatments (Twisk and Maes, 2009). Particularly with recovery, patients with ME and CFS may experience disappointment, frustration, and hopelessness when they do not improve after receiving treatments designed for depression (Friedberg, 2016). Some research has demonstrated psychological treatments, like CBT, to be harmful for patients with ME and CFS (Twisk and Maes, 2009), but helpful for patients with depression (Friedberg and Krupp, 1994).

A useful discriminator for differentiating depression and ME and CFS is how patients react to exercise. Patients with ME and CFS experience post-exertional malaise following exercise (Fukuda et al., 1994), whereas patients with depression experience gains in their mood (Dimeo et al., 2001). Researchers and practitioners could also use the Beck Depression Inventory for Primary CARE (BDI-PC; Beck et al., 1997) to screen for depression among patients with ME and CFS. Compared to the BDI-II (Beck et al., 1996), the BDI-PC is more likely to better measure depressive symptoms in ME and CFS populations due to its omission of overlapping somatic symptoms (Brown et al., 2012b).

Concurrently, we acknowledge that ME and CFS may be comorbid with depression. One review reported a 50–75 percent lifetime history of major depressive disorder in patients with ME and CFS (Afari and Buchwald, 2003). Often, the experience of ME and CFS may lead to depression due to losses in functioning (Jiménez Ortiz, 2015), a common experience

among individuals with chronic illnesses (Smith, 2015). In these cases, it is important to differentiate functional gains in depression from functional gains in ME and CFS. Symptoms such as post-exertional malaise, unrefreshing sleep, and impaired memory have been shown to help discriminate ME and CFS from depression (Hawk et al., 2006), whereas feelings of worthlessness, guilt, and loss of interest in activities (anhedonia) are more likely to characterize depression (Rowe et al., 2017).

Reaching a consensus on case definitions would also lead to more homogenous samples. A review article identified 20 case defintions that researchers have used throughout the years (Brurberg et al., 2014). Brurberg et al. (2014) concluded that few of these case definitions were rigorously validated, and future reviews and treatment studies could evaluate the usefulness and distinctions of these criteria. Empirical work has demonstrated that case defintions play significant roles in selecting for more or less severe individuals (Jason et al., 2016). For instance, Jason et al. (2017) found that a newly proposed research criteria selected more impaired individuals than the Institute of Medicine (IOM, 2015) clinical criteria, in part because the IOM criteria consider certain fatiguing illnesses to be comorbid that other case definitions deem exclusionary (e.g. Major Depressive Disorder with melancholic features). Given our physician experiences, we recommend that researchers employ more stringent case definitions to capture a more homogenous group.

The third challenge to studying recovery concerns sampling bias in research—selecting sick individuals and missing those who recover. This challenge will likely persist until the field has a better understanding of the course of ME and CFS (Cairns and Hotopf, 2005; Nisenbaum et al., 2003). This endeavor requires time and funding to conduct community-based, longitudinal studies. Unfortunately, funding is notably deficient in the ME and CFS field (Dimmock et al., 2016). One feasible direction for future projects is to track convenience samples recruited from medical practice, such as Brown et al. (2012a)’s follow-up study. While these designs suffer from selection bias, they provide practical methods for understanding the course of ME and CFS and how patients conceptualize recovery.

Finally, our sample identified patient coping as a challenge to measuring recovery. Effective coping may mask symptoms, giving the impression that a patient is healthier than their true health status. Although coping may lead to effective illness management, the patient would not be labeled recovered (Devendorf et al., 2017). This suggestion highlights the need to screen for coping behaviors to improve accuracy when reporting recovery.

This study provides important considerations for studying recovery. Our study adds to the literature through providing the physician perspective on this relatively understudied topic, making our findings relevant to both research and practice. However, the limitations of our study should be noted. First, our findings are limited by the small sample size, which may not generalize to the opinions of other physicians. Other physicians may not perceive our findings to be challenges, or, there may be challenges that were not expressed in our sample. It is also possible that others may disagree with the proposed solutions presented in our findings. With this limitation noted, 10 of the participants are ME and CFS specialists, who have served on advisory committees, received large-scale grants, and published extensively

in the field. While our sample included three non-specialists, these physicians noted similar challenges as the specialists.

The second limitation concerns the participants' characteristics. Our sample did not allow for comparison among medical specialties to assess variations in opinions. This was evidenced in the differing views of the two psychiatrists, who viewed ME and CFS as depression variants.

Including these perspectives highlights an important challenge for the field—etiological viewpoints affect how physicians assess ME and CFS. Future studies should recruit larger, more purposive samples that allow for analysis between medical specialties.

The third limitation is our phone-based interview approach. There are concerns that phone-based interviews risk losing rapport, participant motivation, and important visual cues (e.g. gestures). However, a review found little evidence to support these concerns, and phone interviews may facilitate participants to disclose sensitive information more freely (Novick, 2008). Regardless, other qualitative approaches should be considered. Conducting in-person focus groups with physician samples could facilitate constructive discussion about approaching recovery.

To conclude, we acknowledge that the scope of this study is limited by its descriptive nature, and we anticipate the application of these suggestions will look different in research and practice. For instance, assessment in research settings will be constrained by the challenges of data collection, budgeting, and participant retention, whereas practitioners have more flexibility with tracking their patients. Our hope is that future work will acknowledge these considerations when setting patient goals, drafting recovery criteria, and interpreting treatment outcomes.

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Table 1

Additional descriptive quotes for each theme.

Theme	Additional descriptive quotes
Lifespan differences in the illness experience	"A second problem is some researchers have used the wrong control group to compare ME/CFS subjects to. In the PACE trials, the authors used the SF-36 physical functioning scores of the overall UK population to compare their ME/CFS subjects to rather than a healthy age-matched population. The average age of the PACE ME/CFS subjects was in the late 40s to 50 but the overall UK population norms included subjects that were sick or over the age of 65 so the norm was artificially low. It does not make sense to compare the scores of 45–50 year olds to someone much older." (P6) "Well, I believe that young people who have the onset following an infection, like Mono, nearly all get better. But, when a forty-five year old woman gets it, her prognosis for total recovery—in the patients that I see—is poor." (P11)
The heterogeneity of ME and CFS—case definitions, etiological stance	"I believe CFS is an 'umbrella' term that likely has under it some known psychological causes and not-yet-discovered physical causes. Patients who attribute their CFS to a psychological cause and in fact have a psychological cause may be more likely to recover since psychological treatments are effective and available compared to patients who truly have a physical cause and need a biological solution to their illness." (P6) "So to answer your question, if the person had paralytic polio infection entering the left leg, you could ask that question. But if you're asking questions, 'What's the recovery rate of chronic fatigue syndrome/ME?' When these are just un-diagnosed people." (P7)
Patient follow- up and selection bias	*"Interviewer: But to the best of your ability, what percent of patients have recovered or gotten significantly better?* 'Well once again, I can't tell you … I, I, don't see them for long … I see them one time, and that's it.'" (P10) "[W]hen you're in the practice of medicine and a patient disappears from your practice, is it because she got better or because she didn't like you as a doctor? You don't know the answer to that, you know, unless you make phone calls. That would be a very interesting research project: to call my patients over time, and ask how have they done." (P11)
Assessment logistics	"So, the wellness scores are really quick, easy to administer, well understood scale. Umm, some of the patients overestimate their function in the very beginning, so there's a bit of learning that's involved in it." (P4) "[N]obody wants to see these patients. They take forever, they don't really have anything on a physical exam, all their lab tests are normal, and the parents are very worried about the children, the kids, obviously." (P8)