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Onset Patterns of Chronic Fatigue Syndrome and Myalgic Encephalomyelitis:

A Mixed Method Approach

A Dissertation

Presented in

Partial Fulfillment of the

Requirements for the Degree of

Doctor of Philosophy

BY

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Biography

The author was born in Sterling, Virginia, September 15, 1984. She graduated from Park View High School in 2003 and she received her Bachelor of Arts degree in Psychology from The University of Virginia in 2007, and a Master of Arts degree in Clinical Psychology at DePaul University in 2012. She is currently completing her Predoctoral Internship in Clinical Psychology at Children's National Medical Center in Washington, D.C.

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Abstract

Chronic fatigue syndrome (CFS), Myalgic Encephalomyelitis (ME) and Myalgic Encephalomyelitis/chronic fatigue syndrome (ME/CFS) refer to a debilitating illness without a universally accepted or well-understood etiology. Some experts have suggested that there are multiple pathways to the development of ME and CFS, which may also indicate multiple onset patterns. Due to unanswered questions regarding etiology, the onset of ME and CFS is considered a key area of inquiry.

Case criteria for ME and CFS and much of the academic literature suggest that patients typically experience one of two possible onset patterns: sudden or gradual. Many experts consider the mode of ME and CFS onset an important factor for differentiating patients on key dimensions including etiology, health status, prognosis, and psychiatric comorbidity. Previous literature has suggested a link between sudden ME and CFS onset and a viral/infectious etiology, lower psychopathology, and worse health outcomes. However, other studies have found opposite or inconclusive findings. In order to replicate and build on previous research, the current study is an investigation of whether mode of onset differentiates individuals with ME and CFS on etiology, psychopathology, and daily functioning. It was hypothesized that individuals with sudden onsets would more likely report that a virus/infection preceded their illness, attribute their illness to physical causes, evidence lower lifetime psychiatric comorbidity, report poorer physical functioning, and have better mental health outcomes compared to the gradual onset group. Hypotheses were tested using multivariate analyses of

variance (MANOVA) and the Pearson's chi-squared test of independence. Results revealed that mode of illness onset did not differentiate individuals on key factors related to etiology, psychopathology, and prognosis.

The lack of a universal definition for mode of illness onset is likely contributing to the inconsistencies in the percentage of sudden versus gradual ME and CFS onsets reported in the literature. Given the ambiguous etiology, complex symptom profile, and heterogeneous onset patterns associated with ME and CFS, it would be useful to better define onset. An in-depth investigation of ME and CFS onset can provide insight into early symptoms, onset duration, and the progression of functional disability. Few studies have utilized qualitative inquiry to understand the patient's perspective of onset. Based on previous research documenting the rich information that can be gained from personal illness narratives, the second phase of the study involved phone interviews with individuals with ME and CFS. A qualitative descriptive approach was used to gain rich descriptions of illness onset from the patients' point of view. Overall, qualitative findings revealed detailed descriptions of ME and CFS onset experiences. Major themes that emerged from the data included: onset/illness progression patterns, illness causes, methods of adapting and coping, hardworking and active lives prior to onset, healthy lives prior to onset, prior health problems, comorbid health conditions, emotional responses to onset, exertional effects, the illness as life limiting, stress, traumatic experiences, lack of support, support, and treatment limitations. A closer examination of the onset/illness progression patterns that emerged from the data provided evidence that individuals with ME

and CFS experience complex onset patterns. Furthermore, the study findings suggest that the method of categorizing individuals into sudden versus gradual onset groups may not be useful as it fails to capture the more nuanced and varied onset experiences. Prospective research studies that capture the onset period as it is developing could lead to improvements in the way we define and assess ME and CFS onset, and may also lead to methods for early detection, prevention, and individualized treatment approaches for this multifaceted and debilitating illness.

Onset Patterns of Chronic Fatigue Syndrome and Myalgic Encephalomyelitis:
A Mixed Method Approach

Chronic fatigue syndrome (CFS) is a highly complex illness that results in significant disability (Tiersky et al., 2001) and a considerably diminished quality of life (Anderson, Ferrans, & Estwing, 1997). The most widely used case criteria for CFS was developed by Fukuda et al. (1994) and it defines CFS as the experience of six months of severe fatigue in concurrence with at least four out of eight specified symptoms (e.g. memory and concentration impairment, sore throats, tender lymph nodes, muscle pain, joint pain, headaches, unrefreshing sleep, and post-exertional malaise). The Fukuda et al. (1994) criteria also stipulate that individuals affected with CFS are severely impacted in their ability to function in many areas of their lives. CFS is also associated with and frequently referred to as Myalgic Encephalomyelitis (ME; Carruthers et al., 2011), Myalgic Encephalomyelitis/chronic fatigue syndrome (ME/CFS; Carruthers et al., 2003), and myalgic encephalopathy (Shepherd & Chaudhuri, 2001). In addition to the Fukuda et al. (1994) case definition of CFS, three major case definitions in the field are the Carruthers et al. (2003) clinical case criteria for ME/CFS, the Carruthers et al. (2011) International Consensus Criteria for ME, and the most recent Institute of Medicine (IOM) Diagnostic Criteria for Systemic Exertion Intolerance Disease (SEID; Institute of Medicine, 2015). Unlike the Fukuda et al. (1994) criteria, Carruthers et al. (2003; 2011) and the IOM (2015) require the presence of cardinal symptoms for the illness, such as post-exertional malaise. The etiology of ME and CFS is not well understood, and a specific cause has not

yet been established. There are different proposed theories regarding the factors that might precipitate onset, including theories relating to possible viral or infectious triggers, environmental triggers, stressful events, or a combination of these factors (Komaroff, 1988, 1994; Salit, 1997). It has been suggested by some that there may be different pathways leading to the development of symptoms associated with CFS (Jason, Corradi, Torres-Harding, Taylor, & King, 2005; Salit, 1997). Due to continued questions regarding etiology, the period of onset for the illness is of considerable interest to researchers in the field. Much of the literature on ME and CFS related to onset suggests that individuals experience either a sudden/acute onset in which symptoms appear over a short period of time (e.g. a few hours, days, or weeks) or a slower, gradual onset in which symptoms may develop over a period of months or even years (Komaroff, 1998). There is not yet a universal definition for assessing mode of illness onset (sudden versus gradual), and this is reflected in the varying language used across ME and CFS studies and case definitions.

Illness Onset-HIV and MS

The onset of clinical symptoms is considered an important phase of illness development for many chronic illnesses, including those with a known cause, such as acute human immunodeficiency virus (HIV), and illnesses without a clear identifiable cause, such as Multiple Sclerosis (MS). In an effort to better understand how illness onset periods are characterized, it can be beneficial to study a chronic illness such as HIV, which has a well-defined viral and immunological etiology. While previous research has linked ME and CFS to a

viral etiology (Ablashi et al., 2000; Beqaj, Lerner, & Fitzgerald, 2008; Chapenko et al., 2006; Chia, 2005; Holmes et al., 1987; Levine, 2001) as well as to immune dysfunction (Broderick et al., 2010), there is not a universally agreed upon cause for ME and CFS. Therefore, it is also beneficial to study the onset patterns of other chronic illnesses of unknown origin, such as MS. The identification of initial clinical features and symptoms, as well as the chronological timeline associated with onset is important, as it can contribute to the development of effective methods for early detection, diagnosis, and treatment.

Acute human immunodeficiency virus (HIV) infection is a disease with a well documented progression. The initial onset phase occurs after a person is exposed to HIV. As many as 50 to 90 % of individuals who contract HIV develop symptoms (e.g. fever, fatigue, myalgias/arthralgias, rash, and headaches) within one to four weeks after transmission, which can persist for approximately two to four weeks. At this early phase it can be difficult to diagnose HIV infection since it is characterized by symptoms that are also associated with other illnesses including Epstein-Barr virus and influenza. Tests that are available to detect HIV following infection include the HIV RNA viral load (detected within 11 to 12 days of infection), the p24 antigen (detected 14 to 15 days from infection) and HIV enzyme-linked immunosorbent assay (detected within three to eight weeks from infection; Chu & Selwyn, 2010).

Multiple Sclerosis (MS) is a chronic neurodegenerative disorder that causes lesions in the central nervous system (CNS) and disintegration of the myelin sheaths of neurons. A specific cause of MS has not been identified to date;

however, it has been theorized that environmental factors (e.g. infection) in conjunction with genetic risk factors can lead to the development of MS (Compston & Coles, 2008). MS is now considered an organic neurodegenerative disease; however, there was a time when the medical community considered it to be psychogenic in nature and people were often misdiagnosed with the labels hysterical personality disorder or conversion disorder (Feinstein, 2007). Additionally, early theories about the etiology of MS suggested that it was brought on by emotional stress from an oedipal complex or an 'MS-prone personality' (Murray, 1995). Richman and Jason (2001) identified parallels between MS and CFS including the disproportionate number of women affected in both illness populations, as well as the tendency for physicians to associate CFS with psychogenic factors, as these attributions are similar to the early psychogenic theories made by physicians regarding the etiology of MS.

The onset and course of MS is complex. The McDonald criteria and later revisions to this criteria outline different scenarios of illness progression that indicate the presence of MS (McDonald et al., 2001; Polman et al., 2011; Polman et al., 2005). Four of the five scenarios indicate that individuals with MS experience what is referred to as an "attack" or "acute inflammatory demyelinating event in the CNS with a duration of at least 24 hours in the absence of fever or infection" (p. 293). Some scenarios involve only one attack prior to the progression of the illness, whereas other scenarios involve two or more attacks prior to illness progression. A fifth scenario does not require the experience of an attack and involves the insidious/gradual progression of symptoms over the

course of a year. It has also been reported that inflammation of the CNS may occur many years prior to the development of clinical symptoms, further complicating the identification of a clear illness onset (Compston & Coles, 2008). The McDonald criteria (2001) suggest that the onset and progression of MS is varied, providing evidence for subtypes of the illness.

In general, there are challenges to identifying specific onset patterns associated with chronic illnesses. For instance, some illness onsets are characterized by non-specific symptoms that overlap with other chronic health conditions. Additionally, people may experience initial symptoms of an illness without realizing that something is wrong. The identification of initial symptoms and signs may be especially difficult for illnesses of unknown etiology such as MS, as well as ME and CFS. In the case of ME and CFS, there may be multiple pathways to the illness, as has been suggested by researchers in the field (Jason et al., 2005; Salit, 1997), which may also involve different patterns of illness progression.

Illness Onset in Case Definitions of ME, CFS, ME/CFS, and SEID

There is controversy as to whether the illness labels CFS (Fukuda et al., 1994), ME (Carruthers et al., 2011), ME/CFS (Carruthers et al., 2003), myalgic encephalopathy (Shepherd & Chaudhuri, 2001), and SEID (Institute of Medicine, 2015) represent one distinct condition, whether they are part of an illness spectrum, or whether they are simply different terms used to describe the same condition. CFS, ME, ME/CFS, and the recently named SEID, are often associated with different case criteria. Each case definition provides a description of onset,

and while there are similarities across these descriptions, there are some key differences regarding how onset duration is defined across these various definitions.

Early case criteria developed by Holmes et al. (1988) specify that the illness must have a “new onset of persistent or relapsing, debilitating fatigue” without any previous history of similar problems (p. 388). Additionally, Holmes et al. (1988) stipulate that the main symptoms of CFS must occur over a few hours or days, indicating a sudden or acute onset. According to Holmes et al. (1988), symptoms are only met if they begin at the time of the fatigue onset or following onset. Another case criteria for CFS is referred to as the Oxford Criteria (Sharpe et al., 1991) which stipulate that CFS involves a “definite” onset as well as clear evidence of infection at the time of onset or first symptoms. Similar to the Oxford Criteria (Sharpe et al., 1991) the Fukuda et al. (1994) criteria describe the onset of the fatiguing illness as “new” and “definite” (p. 956). The Institute of Medicine (IOM) recently developed a new case definition and renamed the illness as Systemic Exertion Intolerance Disease (SEID; Institute of Medicine, 2015). Similar to the Oxford Criteria (Sharpe et al., 1991) and Fukuda et al. (1994) criteria, the case criteria for SEID specifies that the fatiguing illness is of a “new or definite onset” and not “lifelong.” These vague terms were included in the case criteria in order to exclude individuals who have experienced lifelong fatigue. Reeves et al. (2003) later clarified that the purpose for the requirement of “new and definite onset” fatigue was to exclude those individuals with a primary personality or somatization disorder, which are both characterized as lifelong with

unexplained somatic symptoms. Additionally, Reeves et al. (2003) indicated that it is clinically difficult to identify whether fatigue is “new and definite.” Levine (1997) reported that the requirement for an “acute onset” of CFS was left out of the Fukuda et al., (1994), as Fukuda did not find that the presence of infection differentiated individuals with CFS from those without the illness (Levine, 1997).

The terms Myalgic Encephalomyelitis (ME) and Myalgic Encephalomyelitis/chronic fatigue syndrome (ME/CFS) have corresponding case criteria (see Carruthers et al., 2003; Carruthers et al., 2011), which are different from the Fukuda et al. (1994) criteria in that they require what are considered by many to be key symptoms of the illness (e.g. post exertional malaise and cognitive dysfunction). The Carruthers et al. (2003) criteria for ME/CFS specify that an individual must have a “significant degree of new onset” fatigue (p. 11). Similar to the Holmes et al. (1988) criteria for CFS, the case criteria for ME/CFS stipulate that symptoms can only be counted as meeting criteria if they occur or become significantly worse after the onset of the illness. Carruthers et al., (2003) describe onset as “distinct” and assert that most individuals experience an acute onset; however, they also assert that some individuals are unhealthy prior to their ME/CFS onset and may not be able to identify a specific trigger for the development of ME/CFS, or they may experience a more “gradual” or “insidious” onset (p. 12). Furthermore, Carruthers et al. (2003) suggest that many individuals who experience immune dysfunction experience it most profoundly in the “acute onset stage” and that these symptoms of immune dysfunction fade or come and go as the illness becomes more chronic. According to Carruthers et al. (2003)

individuals with a viral acute onset show more symptoms of immune dysfunction compared to those who report a more gradual onset.

The Carruthers et al. (2003) criteria were created to serve as a guide for health clinician's diagnosing the condition, and the authors suggest that when assessing for the presence of ME/CFS, health care providers should gather information regarding the date of illness onset, the presence of an identifiable trigger or "prodromal event" (p.22), the symptoms present at the time of onset, as well as symptom course and symptom duration. They also provide guidelines for distinguishing ME/CFS from other conditions such as depression and somatization disorders. Additionally, Carruthers et al. (2003) report that one common distinguisher between ME/CFS and depression is the sudden onset common in those with ME/CFS. Furthermore, Carruthers et al. (2003) report that prior to illness onset, individuals with ME/CFS often are active and that the illness onset often follows "acute pro-upper respiratory infections, bronchitis, sinusitis, gastroenteritis, or an acute 'flue-like' illness" (p. 9). Additionally, they discuss prodromal events such as immunization, anesthesia, and pollutant exposure as events that can cause stress on the neuroimmunoendocrine regulatory system. Other possible triggers discussed include trauma or more rarely, a blood transfusion. Carruthers et al. (2003) assert that an affected person will then experience a "progressive decline in health and develop a cascade of symptoms," which occurs "within days or weeks" of the triggering event (p. 9). They further suggest that those who experience gradual progression of the illness are less likely to report "discrete triggering events" (p. 9).

Similar to CFS and ME/CFS, past case definitions of ME have presented varying descriptions of onset. For instance, an early definition for ME by Ramsay (1988) asserts that the onset may be sudden without an identifiable cause, and may be accompanied by acute vertigo. Ramsay reports that there is often a history of infection of the upper respiratory track or sometimes in the gastrointestinal tract in patients with ME. While Ramsey suggested that most individuals with ME experience an acute onset, he suggested that a subset of individuals experience an insidious onset (Dowsett, Ramsay, McCartney, & Bell, 1990).

Hyde's Nightingale Definition of ME (2007) stipulates that ME is both chronic and disabling and is characterized by an acute onset. Additionally, Hyde describes ME as an epidemic or an endemic occurring in two phases (Primary infectious Phase and Primary Chronic Phase). Additionally, Hyde (2007) indicates that ME often follows multiple, minor infections in individuals with susceptible immune systems or immune systems that are weakened by severe stressors (e.g. contact with infectious persons, exhaustion, trauma, immunizations, epidemic disease, travel and exposure to virulent agents). Hyde describes the initial phase of ME as the Primary Infection Phase, which is characterized as an epidemic or endemic infectious disease with an incubation period of between four and seven days. He describes the second phase as the Secondary Chronic Phase, occurring with two to seven days of the Primary Infection Phase. In this phase, Hyde asserts that there are measurable changes in the central nervous system (CNS) of an affected individual and that this phase is the chronic form of the disease that is most commonly depictive of ME. Understanding the cause of ME

can be complicated, as Hyde asserts that all cases of epidemic and primary ME result from an infectious or autoimmune agent, but he also suggests that there are often other potential causes that may go unnoticed prior to the onset of illness or as part of the illness. The presence of other causal factors is also discussed in Goudsmit et al. (2009). With regard to epidemic and primary ME, Hyde suggests that there is a lack of consensus regarding whether there is a viral or infectious etiology of the illness. He suggests that this lack of consensus may be due to the indication that there are patients who experience an acute onset and those that experience a more gradual onset. Hyde suggests that an acute onset is always indicated in a Primary ME patient group whereas a gradual onset may be more indicative of the chronic fatigue syndrome label. Additionally, he expressed the belief that ME is caused by an enterovirus and that those individuals that he has tested for viral infection all experienced an acute onset. While it is not emphasized, Hyde discusses the potential for the development of ME as a result of non-infectious agents (termed Secondary ME), such as exposure to toxic chemicals, which he reported observing in his medical practice. He reports that like Primary ME groups, Secondary ME affects the CNS, and in contrast he suggests that Secondary ME can be more severe.

The International Consensus Criteria for ME (ME-ICC; Carruthers et al., 2011) also provide information regarding illness onset. Carruthers et al. (2011) assert that most patients have an acute infectious onset with flu-like and/or respiratory symptoms, but they also acknowledge that a gradual onset does occur in a subset of individuals. Additionally the ME-ICC criteria recommend that

patients are classified into subtypes based on whether their onset is acute/infectious or gradual, as well as their severity of onset, as this may predict the severity of the chronic course of the illness (2011).

Defining Onset

As is revealed in the various case definitions for CFS, ME, and ME/CFS, the descriptions of illness onset may have some commonalities but also vary in the language and specifications used to differentiate sudden/acute onset and gradual/insidious onset. The lack of a universal definition for mode of illness onset may be contributing to the inconsistencies in the percentage of individuals experiencing sudden versus gradual onset reported in the literature. For instance, some have reported that as many as 91% of a tertiary care sample of individuals with CFS experienced an acute onset following infection (Peterson, Schenck, & Sherman, 1991); whereas other findings taken from community based samples of CFS have found that as many as 63% (Jason et al., 1999) to 77% (Nisenbaum et al., 2003) of individuals endorsed a more gradual or insidious onset of CFS (Jason et al., 1999; Nisenbaum et al., 2003).

In his study of pediatric CFS, Bell (1995) found that approximately 45% of children and adolescents with CFS experienced an acute onset. There may be multiple reasons for the varying reports of onset duration across these studies, including the samples studied (community-based samples versus tertiary care samples). Levine et al. (1992) evaluated individuals who experienced CFS-related symptoms from four separate communities in different parts of the country that had experienced outbreaks of CFS between the years 1984 and 1986, and found

that in three of the communities, the majority of individuals experienced an acute onset, whereas in the fourth community, only 33% experienced acute onset. Other possible reasons for these discrepancies are the use of different case criteria used to select individuals with CFS and different definitions for mode of illness onset. Bell (1995) suggested that the definition used to define sudden and gradual onset may influence the number of participants placed in each group.

There is not one universally used or empirically derived definition of onset duration for ME and CFS. Researchers interested in assessing mode of illness onset have used various definitions. Often, the distinction is made between sudden/acute onset and insidious/gradual onset, but the duration length prescribed to each category differs. For instance, DeLuca, Johnson, Ellis, and Natelson (1997) defined sudden onset for CFS as an unrecoverable “viral-like illness” that could be traced to a definite date. Gradual onset was described as a “slow progression of symptoms over a period of weeks to several months” or longer (p. 85). Participants were classified under these onset definitions based on independent assessments from a physician and a psychologist. When there was disagreement about an onset category they came to an agreement through discussion. In his study of CFS in an adolescent sample, Bell (1995) defined sudden/acute onset as an “abrupt onset of constant and debilitating fatigue that could be dated to a specific event or illness” (p. 45). He described all other onset patterns as gradual. Zheng et al. (2000) utilized a very specific definition of acute infectious-like onset, defining it as occurring over a period of no longer than 48 hours. Mawle et al. (1997) evaluated sudden versus gradual onset CFS groups and

defined sudden onset as “flu-like” and abrupt, over the course of one to two days. Similarly Reyes et al. (1999) described sudden onset as occurring over “a few days” and gradual onset simply as “gradual.” Similar to Deluca et al. (1997), Cukor, Tiersky, and Natelson (2000) defined gradual onset as a “slow progression of symptoms over a period of weeks to months or greater “ and sudden onset as a “viral-like illness with a specific date of onset from which the patient did not recover” (p. 37). Others simply state that individuals with CFS were grouped by sudden versus gradual onset without providing any description of how sudden and onset groups were determined (Nisenbaum et al., 2003). Based on much of the research presented above, there appear to be more specific definitions of acute or sudden onset groups; whereas, gradual groups are often seen as an ‘other’ onset category for onset types that cannot be clearly dated or defined. There does not seem to be any research in the field regarding possible complexities or differences in gradual onset patterns.

Etiology

Onset is considered an important focus of study as it might provide insight into the etiological factors that precede the development of ME and CFS. Numerous studies have investigated links between ME and CFS and potential etiological factors including infections and viruses such as Epstein-Barr virus (EBV; Holmes et al., 1987; Jones et al., 2004; Lerner, Zervos, Dworkin, Chang, & O'Neill, 1997; Levine, 2001; Sairenji, Yamanishi, Tachibana, Bertoni, & Kurata, 1995; Wallace, Natelson, Gause, & Hay 1999; White et al., 1995; Zhang et al., 2010), human herpesvirus-6 (HHV-6; Ablashi et al., 2000; Chapenko et al., 2006; Di Luca et al.,

1995; Levine, 2001; Levine, Eastman, & Ablashi, 2001; Sairenji et al., 1995; Wallace et al., 1999; Yalcin, Kuratsune, Yamaguchi, Kitani, & Yamanishi, 1994), HHV-7 (Chapenko et al., 2006; Di Luca et al., 1995; Levine et al., 2001; Sairenji et al., 1995; Wallace et al., 1999), HHV-8 (Levine, 2001; Levine, Eastman, & Ablashi, 2001), enteroviruses (Chia, 2005; Chia & Chia, 2008; Chia, Chia, Voeller, Lee, & Chang, 2010; McArdle et al., 1996; Swanink et al., 1994; Zhang et al., 2010), and human cytomegalovirus (HCMV; Beqaj, Lerner, & Fitzgerald, 2008; Levine, 2001; Wallace et al., 1999). ME and CFS has also been linked to blood transfusions (De Meirleir, De Becker, & Campine, 1999), chlamydia (Levine, 2001; Nicolson et al., 2000) and mycoplasmal infections (Nicolson, Nasralla, Haier, & Nicolson, 1998). Studies have shown possible links between CFS and parvovirus B19 (Kerr, Cunniffe, Kelleher, Bernstein, & Bruce, 2003), *Coxiella burnetti* (Zhang et al., 2010), and an increased number of D Lactic acid-producing intestinal bacteria (Sheedy et al., 2009). The results of these studies are mixed and there is still not conclusive evidence to provide a causal link between a virus/infection and the development of CFS. Research has also produced evidence for immune dysfunction and damage to the central nervous system (CNS; Broderick et al., 2010). Specifically, studies have found evidence for reductions in natural killer cell signaling and function, abnormal growth factor profiles, decreased neutrophil respiratory bursts, and an increased production of T-helper type 2 (Th-2) cells (Broderick et al., 2010; Cameron, Hirschberg, Rosenberg-Hassan, Ablashi, & Lloyd, 2010; Carlo-Stella et al., 2006; Fletcher, Zeng, Barnes, Levis, & Klimas, 2009; Fletcher et al., 2010; Klimas, Salvato, Morgan, &

Fletcher, 1990; Lorusso, Mikhaylova, Capelli, Ferrari, Ngonga, & Ricevuti, 2009; Mikhaylova, DeRuyter, Rummens, Bosmans, & Maes, 2007). Additionally, there has been evidence for a link between CFS and chemokines and T lymphocytes, as well as a dysregulation of the antiviral ribonuclease L (RNase L) pathway (De Meirleir et al., 2000; Nijs, De Meirleir, Meeus, McGregor, & Englebienne, 2004; Nijs, & Frémont, 2008; Snell, Vanness, Strayer, & Stevens, 2005; Suhadolnik et al, 1997). Jason, Porter, Herrington, Sorenson, and Kubow (2009) have also presented evidence for the role of kindling to the limbic-hypothalamic-pituitary axis as well as oxidative stress in the development and maintenance of ME and CFS.

In addition to biological causes, researchers have investigated the link between stressful life events and the development of ME and CFS. Specifically, some research has found evidence that individuals with CFS experience a higher number of stressful life events prior to their illness onset compared to matched controls (Hatcher & House, 2003; Salit, 1997; Theorell, Blomkvist, Lindh, & Evengård, 1999). For instance, Salit (1997) found that in 39% of a CFS sample, a non-infectious event was reported as occurring prior to illness onset, and these non-infectious events included trauma (e.g. a car accident), allergic reactions, and surgery. A case-control study by Hatcher and House found that individuals with CFS reported more stressful events and difficulties three months and one year prior to the development of CFS (2003). In another case-control study, Theorell et al. (1999) found that individuals with CFS were almost twice as likely to report a negative event within the three months prior to the development of CFS compared

to a control group. Salit (1997) and others have suggested that the cause of CFS is multi-factorial in nature and that a virus or other type of infection may trigger CFS after a person has experienced multiple stressful events.

ME and CFS Onset Subtypes

Many researchers have suggested that mode of illness onset is potentially important for sub-typing individuals with ME and CFS (DeLuca et al., 1997; Jason et al., 2005; Levine, 1997). Onset type may be associated with a variety of factors including etiology, illness severity, prognosis, psychopathology, and symptom profiles.

Onset and Etiology

Some researchers have sought to make a connection between onset type and etiological factors. For instance, a sudden/acute onset of symptoms following previously good health has been associated with a viral or infectious onset (Komaroff, 1988, 1994; Hay & Jenkins, 1994). Salit (1997) investigated both biological and environmental precipitating factors for CFS and found that in 72% of the study sample CFS symptoms developed following an acute infectious illness, involving the presence of distinct flu-like symptoms including a fever, malaise, headaches, and respiratory difficulties. Participants reported that their experience of fatigue became apparent after the flu-like symptoms dissipated. An infection (EBV-2; B. burgdorferi-2; B. abortus-1; Influenza-1; Herpes simplex-1 and Herpes zoster-1) was found in only 23% of participants reporting an infectious onset.

Researchers in the field have examined the presence of stressful life events prior to the onset of CFS (Ray et al., 1995; Salit, 1997; Theorell et al., 1999). Salit found that those with an acute and clearly defined precipitating event (e.g. infection) had an equal number of stressful life events as those in the gradual group prior to the development of CFS (1997). When compared to controls, individuals with CFS, regardless of onset status, reported a higher number of stressful life events prior to CFS onset. In contrast to Salit's findings (1997), MacDonald et al., (1996) did not find an increase in life stress in the year before the onset of CFS. Salit has suggested that multiple factors are responsible for the development of CFS (1997), and if just one factor was contributing to the development of CFS, the types of symptoms and the mode of onset would be more uniform.

Onset and Prognosis

Some studies have found that patients with an acute onset may have a better prognosis than those with gradual onset (Levine, 1997; Masuda Nakayama, Yamanaka, Koga, & Tei1., 2002a; Salit, 1997). However, findings are mixed regarding the extent to which illness onset is predictive of prognosis in individuals with CFS. Jason et al. (2000) found that sudden illness onset was associated with poorer outcomes compared to those with a gradual onset. Reyes et al. (1999) found that over time, symptom patterns among individuals in the sample became more similar for those with sudden and gradual onset and that probability of recovery was not affected by mode of onset. Hill et al. (1999) also found that mode of illness onset was not predictive of a positive or negative illness outcome.

Njoke, Jason, Porter, and Brown (2009) reported that individuals with a sudden illness onset had significantly lower physical functioning and higher fatigue severity compared to those with gradual illness onset.

Some researchers have investigated whether there is an interaction effect for mode of illness onset and psychiatric comorbidity in predicting health outcomes including symptom severity and functioning. Specifically, Njoku, Jason, Porter, and Brown (2009) examined mode of CFS onset and psychiatric comorbidity and found that those individuals with a sudden illness onset and without psychiatric comorbidity had higher rates of fatigue severity and more physical impairment than those with sudden illness onset plus psychiatric comorbidity. Furthermore, they found that those with a gradual illness onset plus psychiatric comorbidity demonstrated higher fatigue severity.

Onset and Psychopathology

Jason et al. (2005) suggest that individuals with CFS often experience a sudden onset, which helps to differentiate the illness from depression, which more often is characterized by a gradual progression. In support of this assertion, DeLuca et al. (1997) found that individuals with CFS who experienced a gradual onset had significantly higher occurrences of Axis I, psychiatric diagnoses than those with an acute onset. Also in congruence with DeLuca and colleagues (1997), Salit (1997) reported that those with an acute CFS onset were less likely to endorse depressive symptoms. Johnson et al. (1999) suggested that there might be two different CFS subgroups; one with sudden onset, without psychopathology, and with serious cognitive impairments, and the other with a slow or gradual

onset of symptoms, psychiatric comorbidity, and mild cognitive impairment. Other researchers have not found any evidence that sudden versus gradual onset groups differentiate based on psychopathology (Cukor, Tiersky, & Natelson, 2000). When examining a community-based sample of individuals with CFS, Jason et al., (2000) found that sudden onset of illness was associated with higher rates of psychiatric co-morbidity. Reyes et al. (1999) also examined a community-based sample of individuals with CFS and found higher rates of depression in the sudden onset group.

Others have examined personality factors associated with mode of CFS onset. For example, Masuda et al. (2002b) found the individuals who experienced a non-infectious (non-acute) onset were what they described as “more neurotic,” had more chronic stress, and had more family related difficulties than individuals who experienced an infectious/acute CFS onset. Masuda et al., (2002b) found that those who developed CFS following an acute infection were more likely to be social and were characterized as extroverts.

Onset and Somatic Symptoms

In an epidemiology study, Reyes et al. (1999) compared sudden versus gradual onset groups for symptoms present at onset and they found that in the sudden onset group, individuals reported significantly more problems with symptoms related to infection, including sore throats, tender lymph nodes, chills, as well as difficulty thinking or concentrating, and hypersomnia. Similar to findings by Reyes et al (1999), in their randomized community-based sample, Jason, Taylor, et al. (2000) found that those with CFS who experienced a sudden

onset were more likely to endorse more severe sore throat pain and increased fatigue after exercise. DeLuca and colleagues (1997) found that individuals with CFS, regardless of onset, had significantly more cognitive difficulties compared to healthy controls; however, individuals in the sudden group did not differ significantly from the gradual group. In a co-twin control study including 22 pairs of monozygotic twins, in which one twin met diagnostic criteria for CFS and the co-twin was healthy, Claypoole and Noonan (2007) found that of the co-twins with a CFS diagnosis, those with a sudden onset had slowed information processing on a neuropsychological assessment compared to those with a more gradual onset. Other studies however have not demonstrated higher levels of somatic complaints in either sudden or gradual onset groups (Cukor et al., 2000).

Onset and Classification

Mode of illness onset may also be useful in differentiating ME and CFS from illnesses that have some overlapping symptoms, including severe fatigue. Linder et al. (2002) used neural networks to classify patients with chronic fatigue syndrome, idiopathic chronic fatigue, lupus erythematosus, and fibromyalgia. Linder et al. (2002) attained 95% accuracy in correctly identifying individuals with their given diagnosis (sensitivity) and 85% accuracy in correctly identifying individuals who were negative for a specific diagnosis (specificity). Symptoms that had the highest differentiating accuracy for CFS were those with an acute onset and sore throats. Furthermore, and as mentioned previously, it has been suggested that a sudden onset can help differentiate individuals with CFS from those with primarily depression (Carruthers et al., 2003; Jason et al., 2005) and

those with a psychosomatic disorder (Carruthers et al., 2003), as these often involve a slower and more gradual onset.

Chronic Illness Narratives

The onset of chronic illness has been described by medical sociologists as a ‘Critical Situation’ (Giddens, 1979), a ‘Biographical Disruption’ (Bury, 1982), and a ‘Turning Point’ (Charmaz, 1991) in the lives of affected individuals. Charmaz suggests that individuals experiencing chronic illness learn to partition their lives in a variety of ways, such as separating their ill periods from their healthy periods, their periods of crisis from periods of calm, and their periods of symptom intensity with periods of remission. She asserts that significant events in an individual’s illness experience become “timemarkers” that are then placed within a meaningful illness chronology (1991; p. 57). Roth (1963) discussed the tendency of people to use illness experiences as a way to partition the phases of their lives and to mark time. Furthermore, Roth suggests that even in a period of crisis or uncertainty within the illness experience, people are able to note timemarkers and place them within their illness chronology (1963). Charmaz also describes timemarkers as significant events or “anchor points” (p. 198) that individuals use to evaluate their health status at any given time. The way in which individuals chronicle their illness allows for the discernment of significant events, durations, places, and people within their illness trajectory. She also asserts that adverse experiences within the illness chronology are experienced and recounted repeatedly. While the re-experience of these negative experiences are likely

stressful to the individual, Charmaz suggests that it allows people to identify nuances about their experience that were previously unnoticed (1991).

Charmaz (1991) discusses the utility of medical references and textbooks in outlining typical disease progression, as they allow individuals experiencing chronic illness to anticipate and compare phases in their illness development. However, she points out the difficulty in specifying illness progression when the onset is unknown. She also suggests that individuals who do not have a formal diagnosis for their illness and who experience indistinct symptoms may have illness chronologies that focus on the difficulties they experience with physicians and health professionals who have failed to validate their illness experience. Charmaz describes how chronic illness can unfold gradually and individuals may not notice that anything is wrong until they experience reductions in their ability to function (1991). This suggests that the development of illness may influence one's ability to discern a precise onset. Nonetheless, Charmaz emphasizes that the construction of illness chronologies can allow individuals to notice illness patterns, such as beginning symptoms or signs of the illness that others cannot (1991). The varied experiences apparent in the unfolding of chronic illness (slow and gradual versus sudden and distinct) as well as the tendency of individuals to actively chronicle their illness over time, provides compelling rationale for the importance of using personal illness narratives as a means of gaining rich information about this critical phase of illness emergence.

Individuals tell stories about their lives as a way to make sense of their experiences (Lieblich, Tuval-Maschiach, & Zilber, 1998). The transactional

model proposed by Lazarus and Folkman (1984) is based on the assumption that an individual's cognitive appraisal of their experiences is influenced by characteristics of the person (e.g. their beliefs and commitments), his or her environment, and the interaction of the two. Conditions in the environment can influence the saliency and duration of an event. According to Lazarus and Folkman, person characteristics combined with environmental factors are integrated to form an appraisal (1984). Individuals reconstruct their experiences through this integrative form of cognitive appraisal, and although the reconstructed experience may not be purely objective, it is a representation of an individual's experiences and their attempt to find meaning and coherence (Gilbert, 2002; Lee & Poole, 2005).

Charmaz (1991) and many others have utilized personal narratives as a way to learn more about the experience of chronic illnesses including rheumatoid arthritis (Brown & Williams, 1995), multiple sclerosis (Reynolds & Prior, 2003), systemic lupus erythematosus (Taïeb, et al., 2010), HIV (Ezzy, 2000), chronic obstructive pulmonary disease (Bailey, 2001), cancer (Lee, 2001), and CFS (Hughes, 2002; McCue, 2004).

Qualitative Assessment of Chronic Illness Onset

In-depth qualitative inquiry of the initial stage of chronic illness development from the patients' perspective has been considered a useful approach for examining a variety of illness experiences. Some specific studies include those investigating the early symptoms of lung cancer (Corner, Hopkinson, Fitzsimmons, Barclay, & Muers, 2005), the trajectory of general stroke onset

(Kirkevold, 2002), narrative descriptions of sudden stroke onset (Faircloth, Boylstein, Rittman, & Gubrium, 2005), factors related to the onset of generalized osteoporosis in women (Okma- Keulen & Hopman Rock, 2001), and investigations of symptoms, time course patterns and contributory factors associated with heart failure (Schiff, Fung, Speroff, & McNutt 2003). These authors suggest that an in-depth analysis of chronic illness onset can provide insight into varied onset experiences, potential contributory and exacerbating factors, ways to improve methods for early illness detection, as well as intervention, treatment, and early prevention efforts.

Qualitative Assessment of ME and CFS Onset

Researchers in the ME and CFS field have also utilized a qualitative approach to better understand a variety of experiences related to ME and CFS, including the experience of illness onset. One study by McCue (2004) examined the illness narratives of 14 women who had reported significant improvement or total recovery from CFS. McCue (2004) investigated the personal experiences of illness onset that these women recounted, which included their difficulties receiving a diagnosis, the lack of attention to physical symptoms by their doctors, the tendency to assume a psychological etiology, and the significant stigma they experienced by the medical community.

Reconstructing Events of ME and CFS Onset

Others have investigated illness narratives of ME and CFS onset with an emphasis on how people account for the initial unfolding of their illness in terms of patterns of onset and the perceived etiological factors and stressful events that

co-occurred with onset (Ray et al., 1998). Ray et al. (1998) interviewed 60 adults out of a larger subset of 147 adults who met the Oxford Criteria (Sharpe et al., 1991) for CFS and asked them to describe their illness onset. Ray et al. (1998) prompted participants by asking whether they had a gradual or sudden onset and asked them to describe in detail their onset duration as well as perceived contributory factors. Additionally, they interviewed participants with the shortest illness durations as well as individuals with the longest illness durations to investigate how illness length impacts their perception of onset and contributory factors. Interviews were coded for perceived contributory factors as well as how participants perceived the early development of their illness. The authors reported that the designated coders focused on how participants described their initial illness progression and they did not limit their coding to the terms “sudden” or “gradual.” Three separate groups of participants were identified when coding for CFS onset. One group was characterized by a gradual onset of CFS in which there was a slow, worsening of symptoms over time, culminating into the attribution that the illness was serious (n=15). A second group was identified as having an acute onset, which was characterized by a sharp increase in symptoms (n=31). Lastly, a third group was identified as having a two-phase illness onset, which began with a sharp deterioration and subsequent improvement in phase one, that was then followed by another deterioration of symptoms in phase two (n=14).

Ray et al. (1998) examined differentiating themes across the onset groups and found that individuals in the gradual onset group attributed their illness to an infection or a series of infections, antibiotics, and the immune system “breaking

down.” More complex accounts included a combination of infection, overexertion, and stress. The sharp onset group described a clear transition between health and becoming ill, and one participant described going “down with a bang” (p. 103). Individuals in the sharp onset group listed similar contributory factors as the gradual group. The phased onset group largely reported that an infection was the trigger of their illness. Within this group, one participant reported that “there was a gap and then it re-appeared” (p. 104). In 11 cases, a worsening of illness was attributed to “overdoing things” (p. 104). Some reported a failure to allow themselves time to recover. Additional findings by Ray and colleagues (1998) revealed strong and significant associations between illness duration and onset characteristics, as longer duration of illness (56-72 months) was associated with a gradual onset, and shorter duration (seven to 22 months) of illness was associated with sudden onset. This suggests illness duration can influence an individuals’ representation of their onset pattern.

Phases of Chronic Illness and the Fennel Phase Theory of CFS

Stage models have been proposed to describe the progression of chronic illness, always beginning with an initial, onset stage. One stage model developed by Rest (1971) suggests that chronic illness patterns involve the progression through distinct stages within a developmental sequence. Stages are hierarchical under this model, which assumes that an individual progresses through the stages in a successive manner so that each stage builds on a previous stage. Another stage model developed by Kubler-Ross (1969) proposes stages of illness that are

not discrete or in any hierarchical and fixed sequence. The stages in the Kubler-Ross model (1969) can overlap and be experienced in any order.

Fennell (1995) has applied a model of stage theory to describe the experience of CFS. Fennell proposed a phase model of CFS in which individuals living with the illness progress through four different stages of coping. The initial phase of Fennell's model involves the "crisis mode" immediately following the onset of the illness. Fennell describes this stage as the period in which an individual experiences the initial emotional trauma of the emerging illness. Phase two of the model involves continued disruption and disorder followed by a stabilization of symptoms. Subsequently, phase three involves a sense of resolution by the sufferer, in which an acceptance of the chronic nature and ambiguity of CFS is more or less accepted by the individual. Lastly, phase four is described as a period of "integration" in which a person is able to integrate their pre-illness identity with their post-illness identity (1995).

Fennell's phase theory of CFS is aligned with Kubler-Ross' theory of death and dying, as it describes the experience of CFS and other chronic illnesses as continuous and cyclical in nature, such that individuals do not necessarily experience phases in a fixed order. Fennell proposed stage theory as a way to describe the progression that individuals take in their ability to cope with and come to terms with the illness; however, stage theory may also be beneficial for identifying the specific events and characteristics that define these stages, including factors related to symptom and stage duration, emerging symptoms, and illness-related consequences such as a loss of functioning.

Jason et al. (1999; 2000) utilized factor analytic methods to evaluate an instrument designed to measure the phases experienced by individuals with CFS (Fennell Phase Inventory; FPI) and found evidence of three distinct factor scores that adequately characterized the Crisis, Stabilization and Integration phases proposed by Fennell. Furthermore, the three factor scores were utilized in a cluster analysis, which resulted in four distinct clusters that reflected the four Fennel phases: Crisis, Stabilization, Resolution, and Integration. The development of the FPI and the empirical support for distinct phases of CFS has allowed a more in-depth look at the psychological and physiological processes occurring at these different phases. Reynolds, Brown, and Jason (2009) explored how the FPI was related to physical and psychological functioning and coping style. Results showed that individuals in the crisis phase had poorer functioning related to depression, quality of life, mental functioning, anxiety, and self-efficacy, as well as less adaptive coping styles. Those in the resolution phase maintained the most adaptive coping strategies. Fennell described distinct phases of CFS-related coping and adaptation. It is possible that Fennell's phase theory can provide a theoretical foundation for documenting and evaluating the experience of CFS onset beyond just coping and adaptation. Other factors that may provide insight into this initial period of illness development may include bodily sensations/somatic symptoms, functional disability, and duration.

Rationale

ME and CFS are a complex and debilitating illness without a conclusive or universally accepted etiology. It has been suggested that the ME and CFS label

involves multiple illness types with both distinct and overlapping features, and this is problematic for classifying individuals based on common features (Jason et al., 2005). Due to the heterogeneity of the illness, it has been suggested that there may be subtypes of people within the ME and CFS diagnostic construct (Jason et al., 2005). One potentially important factor for differentiating people with ME and CFS is mode of illness onset; specifically, whether the illness developed in a sudden or a gradual manner (DeLuca et al., 1997; Jason et al., 2005; Levine, 1997). The mode of ME and CFS onset may differentiate individuals on key factors including etiology, prognosis/health status, and psychopathology. For instance, previous research has demonstrated a potential link between sudden CFS onset and a viral/infectious etiology (Komaroff, 1988, 1994; Hay & Jenkins, 1994; Salit, 1997). Sudden CFS onset has also been associated with a lower prevalence of psychopathology prior to onset, compared to gradual onset patterns (DeLuca, Johnson, Ellis, & Natelson, 1997; Johnson et al. 1999; Salit, 1997). Additionally many have theorized a possible link between mode of illness onset and health status. Some studies have found that patients with a sudden onset have a better prognosis than those with gradual onset (Levine, 1997; Masuda Nakayama, Yamanaka, Koga, & Tei, 2002a; Salit, 1997), while others have found that sudden illness onset was associated with poorer outcomes related to physical functioning (Jason et al., 2000), as well as symptom presence and severity (DeLuca et al., 1997; Jason et al., 2000; Njoke et al., 2009; Reyes et al., 1999) compared to those with a gradual onset. These findings are mixed and some

researchers have failed to find a link between CFS onset and prognosis (Hill et al., 1999; Reyes et al., 1999).

There continues to be controversy in the field with regard to the mixed evidence linking CFS onset with etiology, prognosis, and psychopathology. Additionally, the samples used in past studies were small; therefore, more research in this area with larger study samples is necessary. In an effort to build on previous work, the current study serves as an investigation into whether those with a sudden illness onset are differentiated from those with a gradual onset on these key factors. Based on previous research linking CFS sudden onset with an infectious etiology, poorer health outcomes, and lower psychiatric comorbidity, it is expected that those with a sudden onset will more likely report that a virus or infection preceded ME and CFS, will more likely attribute their illness to physical causes, will have lower lifetime psychiatric comorbidity, poorer physical functioning outcomes, and better mental health outcomes compared to those with a gradual onset.

Given the ambiguous etiology, complex symptom profile, and the heterogeneous onset patterns associated with ME and CFS, it would be useful to better define the earliest stage of the illness. Fennell's Phase Theory (1995) describes four stages of adaptation and coping associated with the progression of ME and CFS. It is possible that a closer investigation of the Crisis phase (i.e. time of onset) may allow for the operationalization of this initial phase by identifying and clearly defining early symptoms and signs of ME and CFS, as well as the potentially varied patterns at onset, duration of onset, and the extent of functional

disability experienced in this early crisis phase. In order to fully capture the experience of onset, it may be crucial to interview those who are most directly affected by the illness; the patients themselves. Roth (1963) suggests that even in a period of crisis or uncertainty during the illness experience, people are able to note timemarkers and place them within their illness chronology. Charmaz (1991) suggests that illness narratives allow for the identification of nuances of the illness experience that may otherwise not be captured. Illness narratives have also been used to better understand a variety of illness experiences as well as CFS (Hughes, 2002; McCue, 2004).

To this author's knowledge, there are only a small number of studies that have utilized illness narratives for the purpose of examining the initial onset period of CFS. McCue (2004) investigated personal experiences related to stigma and diagnostic difficulties and Ray et al. (1998) conducted qualitative interviews with individuals with CFS and identified the presence of three onset types (sudden, gradual, and phased). The evidence for three onset types suggests that onset may be more complex than the dichotomous way it is often classified in the literature (e.g. sudden versus gradual). A more in-depth look at this early stage of CFS may provide insight into how individuals with CFS account for and describe their illness onset. Based on previous research documenting the rich information that can be gained from personal narratives of illness experience, the current study involved interviews with individuals with CFS to determine how they describe their illness onset.

In sum, a close evaluation of onset patterns of CFS may provide insight into whether mode of illness onset is useful in sub-typing individuals on key factors related to etiology, psychological factors, and prognosis. Furthermore, an in-depth look at CFS illness narratives can illuminate the onset experience, which can help with the further operationalization of the initial crisis phase proposed by Fennel. Operationalization of this early phase of illness could lead to more consistency in how onset is described and documented in the literature, and could also improve our methods for assessing this potentially crucial time period in the development of ME and CFS. Lastly, a more-in-depth examination of ME and CFS onset patterns may lead to more effective methods for early detection of this devastating illness.

Statement of Hypotheses and Research Questions

Hypothesis I. Individuals with a sudden ME and CFS onset (24 hours to 1 month) will more likely report that an infection or virus preceded their fatigue/energy problems than individuals with a gradual onset (2-6 months to 3+ years).

Hypothesis II. Individuals with a sudden ME and CFS onset will more likely report that the cause of their fatigue/energy problems is “Definitely Physical” or “Mainly Physical” than individuals with a gradual onset.

Hypothesis III. Individuals with a sudden ME and CFS onset will evidence higher role emotional (role limitations due to personal or emotional problems) and mental health functioning than individuals with a gradual onset.

Hypothesis IV. Individuals with a sudden ME and CFS onset will have lower rates of lifetime psychiatric comorbidity than individuals with a gradual onset.

Hypothesis V. Individuals with a sudden ME and CFS onset will evidence lower physical and role physical functioning than individuals with a gradual onset.

Research Question I. How do individuals with ME and CFS describe their illness onset, specifically with regard to the early days, weeks, or months in which their illness emerged?

Method

Research Participants and Procedures

The current study involved two phases. In the first phase, participants completed the DePaul Symptom Questionnaire (DSQ), a survey that assesses demographic information, ME and CFS symptomatology, and illness history. In the second phase of the study a subset of phase one participants were asked to complete a semi-structured phone interview regarding their illness onset.

Phase one. An international convenience sample of adults self-identifying as having CFS, ME/CFS, or ME was recruited (Jason, Brown, Evans, Sunnquist, & Newton, 2013; Jason, Sunnquist, Brown, Evans, & Newton, 2014). In order to be eligible, individuals had to be at least 18 years old, capable of reading and writing English, have a self-reported current diagnosis of ME, CFS, or ME/CFS, and meet the Fukuda et al. (1994) case criteria for CFS. Following approval by

DePaul University's Institutional Review Board, participants were recruited from a variety of sources including postings on internet forums and support group visits. Additionally, some participants who participated in previous studies conducted by the DePaul research team or who emailed the research team's email address with an interest in participating in future studies were re-contacted.

Participants were given three options for completing the surveys: an electronic survey, a hard-copy survey, or a verbal survey over the telephone. All participants were given the opportunity to complete these surveys at home or in person at the Center for Community Research at DePaul University. Participants were not given a timeline for survey completion, as this illness can be fluctuating in nature, and a rapid decline of functioning can occur on any given day. The first 100 individuals who completed the survey received a \$5.00 gift card to Amazon.com for their participation.

Of the original 217 individuals who completed the DSQ, 181 participants were included in the present study. Twenty-eight participants were excluded due to active medical conditions, active psychological conditions, and/or the endorsement of lifelong fatigue, all of which preclude a diagnosis of CFS based upon the Fukuda et al. (1994) case definition. Seven participants were excluded due to not meeting full criteria for Fukuda et al. (1994). One participant did not answer the question regarding onset duration and was excluded. Although there was no formal psychiatric interview, Torres-Harding, Jason, Cane, Carrico, and Taylor (2002) have demonstrated that individuals with CFS are capable of validly self-reporting psychiatric comorbidity information.

Demographically, the sample of 181 participants was 83.3% female and 16.7% male. 97.8% of the sample identified as Caucasian, 0.6% as Asian or Pacific Islander, and the remaining 1.6% identified as “Other.” Of those participants who identified as “Other”, three participants identified as Hispanic or Latino origin, and one identified as multi-racial. One participant identified as American Indian or Alaska Native. With regard to marital status, 57.6% identified as married, 0.6% identified as separated, 18.1% identified as divorced, and 23.7% identified as never married. 43.5% of participants endorsed having children. 55.6% of the sample stated that they were currently on disability, with only 11.7% of the sample working part or full-time. With regards to educational level, 40.0% of the sample held a professional degree, 35.0% held a standard college degree, 17.8% attended college for at least one year, and 7.2% completed high school or had a GED. The mean age was 51.53 (SD = 11.30).

Phase two. The second phase of the study involved qualitative interviews with a subset of the larger sample of 181 participants. A total of 14 adults were recruited from the larger sample. Participants in phase two were identified using stratified purposeful sampling (Patton, 2002) based on onset duration. Participants responded to an item on the DePaul Symptom Questionnaire (DSQ) that assesses onset duration (i.e. the period of time in which their illness developed). Possible responses included: within 24 hours, over one week, over one month, over two to six months, over seven to 12 months, over one to two years, and over three or more years. Two people from each of the seven onset duration categories were

recruited to participate in phase two of the study in order to incorporate a broad range of onset experiences.

All 14 participants (13 females and 1 male) identified as Caucasian, nine (64.3%) identified as married, two (14.3%) identified as divorced, two (14.3%) identified as never married, and one individual (7.1%) left the marital status item blank. Six (42.9%) participants reported having children. With regard to work status, seven (50%) participants were on disability, one (7.1%) identified as a student, two (14.3%) identified as homemakers, one (7.1%) was retired, one (7.1%) identified as unemployed, and two (14.3%) reported that they were working part-time. With regard to educational level, four (28.6%) held a professional degree, six (42.9%) held a standard college degree, two (14.3%) attended college for at least one year, and two (14.3%) completed high school or had a GED. The mean age was 53.21 (SD = 9.31).

After receiving IRB approval, researchers emailed an IRB approved consent form to potential participants for phase two of the study. Participants who consented to the study were instructed to reply back to the email with the following message: "I consent to be in this study. I have received the attached document and after reading the document, I understand what will be asked of me during the study and I also understand my rights as a research participant."

After informed consent was obtained, researchers scheduled the phone interview. Interviewers called participants' cell phone or landline phone using the internet calling service Skype. The author/principle investigator (PI) and an IRB approved undergraduate student/research assistant from the Center for

Community Research at DePaul University served as interviewers. The author/PI trained the undergraduate research assistance on administration of the interview protocol and both participated in weekly meetings to review progress and to discuss any issues with scheduling or with the interview protocol.

At the start of the phone interview, the interviewers explained to participants that they would be asked to discuss their health and illness experiences. They were told that the interview would take approximately one hour to complete. Additionally, they were told that the interviewer would ask them follow up questions in order to obtain more detailed information about a particular experience or event. They were also reminded that they did not have to answer any question that they did not feel comfortable answering and they were reminded that they could take breaks at any time during the interview. Additionally, participants had the option of breaking up the phone interview into two separate interviews as the one-hour time commitment was too taxing for some. Participants were also encouraged to tell the interviewer or PI about any questions or concerns they had throughout the study period.

Following the initial introductory statement by the interviewer, interviewers asked participants which illness label (e.g. ME, ME/CFS, and CFS) they preferred to use when describing their illness. This label was then used throughout the interview. The first study question of the interview was open-ended and read as follows: “Please tell me about the period of time when you first became sick with ME/CFS” (or CFS or ME depending on participants preferred illness label). Interviewers proceeded with an open-ended line of questioning (e.g.

“What else do you remember about that experience?”) in order to get rich, detailed information about participants’ perceptions of their onset period. The interview also included an open-ended question that read as follows: “Please tell me about the period of time before you became sick with ME/CFS” (or ME or CFS). Interviewers followed up further with an open-ended line of questioning in order to receive the most rich and detailed account possible from participants: “Please tell me about the year before you became sick with ME/CFS” and/or “Please tell me more about that experience.” The open-ended questioning was adapted for each participant’s unique illness experience; therefore, the interview protocol was semi-structured to allow for flexibility.

Following these open-ended questions, interviewers proceeded with more direct questioning for the purpose of filling in gaps of information that was not provided from the initial open-ended questions and for determining more objective measures of participants’ functioning and disability prior to and following the onset of the illness. Specifically, interviewers asked participants over what period of time their first symptoms developed and what year and month (if remembered) participants became first became ill with CFS. Interviewers asked participants to indicate their level of disability and functioning using a CFS Disability Scale (Bell, 1995) which was emailed to participants prior to the interview. The CFS Disability Scale is an 11-point scale with possible response values from 0-100, where 100 represents normal, fully active functioning, and 0 represents severe disability/unresponsiveness (See description of this scale in the Measures section below). Participants were asked to rate their functioning level

during the time of onset or first sign of symptoms, prior to onset/first symptoms, and the period following onset/first symptoms. In addition to questions about functioning, interviewers asked participants to indicate which symptoms they may have experienced before, during and after onset. Furthermore, interviewers assessed for other significant personal, work, or other health related events that occurred during these timeframes. Interviewers also asked participants to recall significant life events including holidays as well as information regarding the time of year (e.g. seasons) in order to aid participants' recall of their functioning and symptoms at onset. These recall aids are a major component of the widely used and reliable Timeline Follow Back Interview method for the assessments of past alcohol use (Sobell & Sobell, 1992) and has also been used for the assessment of cancer patients' retrospective recall of early symptoms before diagnosis (Corner, Hopkinson, Fitzsimmons, Barclay, & Muers, 2005). The interview allowed for considerable flexibility in questioning, as it was important for interviewers to ask questions based on each participant's unique timeline and illness history.

Following completion of the phone interview, participants were debriefed on the purposes of the study and they were provided with contact information for any further inquiries. The audio-recorded phone interviews were transcribed verbatim and entered into the qualitative data analysis software program NVivo 10.0 (QSR International, 2012).

Qualitative method. The qualitative approach for this study is based off of the principles of qualitative description (Sandelowski 2000; 2010). Qualitative description involves lower-inference interpretation compared to other qualitative

methods such as phenomenological approaches (Sandelowski 2000; 2010). Qualitative description has been identified as particularly useful in the health sciences and health care fields, in mixed-method designs, and for use with vulnerable populations (Neergaard, Olesen, Andersen, & Sondergaard, 2009; Sullivan-Bolyai, Bova, & Harper, 2005). Additionally, it has been described as an appropriate approach when the desired outcome is a rich description of a phenomenon, process, event, or experience. Furthermore, when using a qualitative descriptive approach, the researcher attempts to stay as close to the data as possible without over-interpreting the data from the perspective of the researcher (Neergaard et al., 2009; Sullivan-Bolyai et al., 2005; Sandelowski, 2000). Qualitative description is considered a useful approach for questionnaire/scale development, needs assessments, and for the development or improvement of treatment interventions (Sullivan-Bolyai et al., 2005). This naturalistic approach allowed for the rich description of the current study participants' accounts of the early days, weeks, and months their illness.

The interview transcripts were analyzed using qualitative content analysis. The general analysis steps taken were based on an approach originally described by Weber (1985) and also summarized by Zhang and Wildemuth (2009). Following full transcription of the audio-recorded interviews, the unit of analysis was identified. The interview text was coded by themes, which were expressed in words or phrases. The analysis began with reading and re-reading the interview text in order to gain a full sense of the data. During initial thematic analysis, key words and phrases were identified using an "open coding" approach (Corbin &

Strauss, 2008, p. 160) in order to allow for patterns and themes of onset experience to emerge from the data (Patton, 2002). The text was read repeatedly this way in order to define and develop categories that were included in the coding scheme. This approach is consistent with the naturalistic inquiry that is characteristic of qualitative description (Sandelowski, 2000). A coding manual was developed in order to clearly define and outline categories as they emerged and to enhance reliability across coders (Zhang & Wildemuth, 2009). The coding manual included definitions and rules for assigning categories to the text, and each category included examples of text from transcripts, as suggested by Weber (1990). Coding and category development was ended once the categories were deemed saturated and new information was no longer contributing to the development of new categories or to category refinement (Patton, 2002). A three-stage method for establishing intercoder reliability and agreement (Campbell, Quincy, Osserman, & Pedersen, 2013) was used. In the first stage, the PI and second trained coder implemented the coding scheme on a randomly selected sample of transcripts and then calculated intercoder reliability. In the second stage, coding disagreements were discussed and resolved through a negotiation process among the PI and the second coder, in order to establish a high level of intercoder agreement. In the third stage, the PI then implemented the coding scheme on the remaining transcripts. Campbell et al. (2013) recommend this three-stage method for situations in which one coder has more expertise on the topic being investigated.

Participant responses to interview questions related to functioning/ability levels over time (using the CFS Disability Scale) were used to develop a visual graph of onset chronology, similar to the visual graphs created from the lifeline interview methods of Bourque and Back (1977). Lifeline interviews have been used to construct life timelines that require respondents to draw “up and down” lines that represent the positive and negative periods and events of their lives on a visual graph. Okma-Keulen and Hopman-Rock (2001) utilized and adapted the lifeline interview method in order to gain a richer understanding of characteristics associated with the onset of generalized osteoarthritis in women (2001). In traditional lifeline studies, the visual graphs are completed by the participant or co-constructed by the participant and interviewer. The current study involved phone interviews; therefore, this author completed the onset lifelines after the interviews with participants were completed. The “ups and downs” on the onset graph were graphed on the Y-axis and were constructed using the participants’ responses to disability/ functioning questions (participants responses using the 0-100 disability scores that from the CFS Disability Scale) as well as their report of symptoms and significant life (personal and health) experiences. The visual graphs are different than typical lifeline graphs, as they do not cover a person’s entire life course, rather they focus on the onset period, the year leading up to onset, and the time following the onset period. Some individuals’ histories began years before the onset and others began a year or a month prior to illness onset; therefore, the interview protocol and the visual graphs allowed for these differences in illness experience. The graphs were created using Microsoft Excel.

After the graphs were completed, they were emailed to the respondents in order to check for accuracy. Respondents had the opportunity to provide corrections by replying to the email with a list of corrections and/or additions to the graph, or they could provide their corrections over the phone by communicating to the author which aspects of the graph needed correction.

Following data analyses, this author emailed participants a summary of the major themes and key findings across the overall sample as well as copies of their individual illness timeline graphs. After the summaries were received, participants were provided the opportunity to provide their impressions of the overall themes and findings by replying to the authors' email with thoughts and reflections or by opting to have a second 15-30 minute phone interview. The phone conversation was informal and allowed for a back and forth reflection between author and participant regarding the study and overall impressions.

Measures

The first phase of the study utilized a broad measure of CFS symptomatology, demographic, and illness history, as well as a measure of functional disability. The second phase of the study included a semi-structured interview format, in which participants were asked questions related to their illness onset. The interview also included a measure of functional disability.

DePaul symptom questionnaire. All participants completed the DePaul Symptom Questionnaire (DSQ) (Jason, Evans, Porter et al., 2010), a self-report measure of CFS, ME, and ME/CFS symptomatology, demographics, and occupational, psychiatric, medical and social history. The DSQ was developed to

classify individuals on a variety of CFS, ME, and ME/CFS case definitions; however, the symptom list was based upon a revised approach to the Clinical Canadian criteria for ME/CFS (Carruthers et al., 2003). The DSQ includes questions related to CFS symptoms (including symptoms that preceded the CFS onset), diagnosis, treatments, and psychiatric/medical diagnoses. Participants are also asked to indicate whether they have family members with CFS. Additionally, participants are asked to identify the duration of their illness onset period, the degree to which their illness was caused by physical versus psychological factors, and specific difficulties related to energy, fatigue, and post-exertional malaise. The majority of items on the DSQ have evidenced good to excellent correlation coefficients, suggesting that the overall instrument is a reliable measure for examining symptoms and illness constructs within the patient community (Jason, Brown, Sunnquist, & Evans, 2014). For the purposes of the study, only questions that specifically assessed aspects related to onset duration, infectious events preceding CFS onset, psychiatric comorbidity, and illness attributions regarding the cause of illness were examined. These items are presented below in more detail.

Onset duration. Participants were asked to respond to the following question on an 8-point likert scale: “over what period of time did your fatigue/energy related illness, develop?” Possible responses include: 1= within 24 hours, 2= over one week, 3= over one month, 4= over two to six months, 5= over seven to 12 months, 6= over one to two years, 7= over three or more years, and 8= I am not ill. No participants endorsed that they were not ill. Jason, Brown,

Sunnquist, and Evans (2014) found that this item demonstrated excellent test-retest reliability with a kappa coefficient of .76 when completed by individuals with ME and CFS.

Events preceding CFS onset. On the DSQ, participants were asked to indicate if they experienced a significant event prior to developing CFS. Specifically the item asks: “did your fatigue/energy related illness start after you experienced any of the following? (Check one or more and please specify)”: an infectious illness, an accident, a trip or vacation, an immunization, surgery, severe stress (bad or unhappy event), other, I am not ill. No participants included in the current study endorsed that they were not ill. This study will focus on responses to the infectious illness category of this item. Jason et al. (2014) found that this item category demonstrated excellent test-retest reliability with a kappa coefficient of .90.

Psychiatric comorbidity. With regard to psychiatric comorbidity, participants were asked the following questions: “Have you ever been diagnosed and/or treated for any of the following: Major depression, Major depression with melancholic or psychotic features, Bipolar disorder (Manic-depression), Anxiety, Schizophrenia, Eating Disorders, Substance Abuse, Multiple chemical sensitivities, Fibromyalgia, Allergies, Other (Please specify), No diagnosis/treatment. Participants are instructed to check all responses that apply and to also write in the year the condition was experienced, years it was treated, and medication if applicable. For the purposes of the current study, only responses involving psychiatric diagnoses were examined. Jason et al. (2014) found that this

item demonstrated excellent test-retest reliability with kappa coefficients ranging from .76 to .92 for psychiatric diagnoses as reported by individuals with ME and CFS.

Medical outcomes study short-form 36 survey (SF-36). All participants completed the SF-36 (Ware, Snow, & Kosinski, 2000), a 36-item self-report measure of disability comprised of eight subscales: physical functioning, role physical, bodily pain, general health, role emotional, social functioning, vitality, and mental health. The composite score for each subscale ranges from 0-100, with higher scores indicating better functioning. This measure is frequently used in research to assess disability brought on by illness. Buchwald, Pearlman, Umali, Schmaling, and Katon (1996) found that for a sample of individuals with CFS, the SF-36 had good internal reliability and convergent validity. It was also able to distinguish individuals with CFS and chronic fatigue from individuals with major depression, acute mononucleosis, and from healthy controls.

DePaul onset interview. A semi-structured interview was developed by this author and colleagues at the Center for Community Research at DePaul University (See Appendix A). The Interview includes open ended and close-ended questions that ask participants to describe their illness onset and the year leading up to onset. The questionnaire also includes guidelines for assessing participants' level of disability and functioning at onset, prior to onset, and following onset. For participants who are not able to identify a clear onset, interviewers asked participants about the period of time in which they experienced the first symptoms/signs of the illness. The interview also assesses

any significant personal and health-related events, as well as symptoms experienced before, during, and after illness onset. The questionnaire allows for flexibility and for follow up questions in order to capture each participant's unique illness timeline and to gain detailed information on onset and functioning.

CFS disability scale. The CFS Disability Scale (See Appendix B) was developed by Bell (1995) as a tool for physicians and other health clinicians to assess disability level and activity reduction. The CFS Disability scale is a modified version of the Karnofsky performance scale (Karnofsky, 1949), which was developed for the purpose of quantifying the functional status of individuals with cancer. Similar to the Karnofsky scale, the CFS Disability Scale is based on an 11-point scale from 0-100 (with 10 point increments), where 0= unresponsive and 100=fully active/normal. To this author's knowledge there are no studies published that have examined the reliability and validity of the CFS Disability Scale.

Results

Phase One

Quantitative analyses were conducted in order to determine whether mode of illness onset (sudden versus gradual) differentiated individuals with ME and CFS on key factors related to etiology, psychological factors, and prognosis.

For Hypothesis I, it was predicted that individuals with a sudden ME and CFS onset (24 hours to 1 month) would more likely report that an infection or virus preceded their fatigue/energy problems compared to individuals with a gradual onset (2-6 months to 3+ years). Results of the Pearson's chi-squared test

of independence revealed that the percentage of participants who reported that an infection preceded their illness did not differ by onset group, $\chi^2(1, N = 181) = 1.10, p = .29$ (see Table 1 for frequency and percentage by onset group).

For Hypothesis II, it was predicted that individuals with a sudden ME and CFS onset would more likely report that the cause of their fatigue/energy problems is “Definitely Physical” or “Mainly Physical” than individuals with a gradual onset. Results of the Pearson’s chi-squared test of independence revealed that the percentage of participants who reported that the cause of their illness was “Definitely Physical” or “Mainly Physical”, did not differ by onset group, $\chi^2(1, N = 178) = .91, p = .34$ (see Table 1 frequency and percentage by onset group).

For Hypothesis III, it was predicted that individuals with a sudden ME and CFS onset would evidence higher role emotional and mental health functioning than individuals with a gradual onset. A multivariate analysis of variance (MANOVA) was performed to examine whether sudden onset mean scores on the Role Emotional and the Mental Health sub-scales of the SF-36 are significantly higher than the gradual onset mean scores. There was not a clinically significant main effect of onset group on mental health functioning; however, a trend was noted in the expected direction, $F(2, 181) = 2.89, p = .06$ (see Table 2 for means and standard deviations by onset group).

For Hypothesis IV, it was predicted that individuals with a sudden ME and CFS onset would have lower rates of lifetime psychiatric comorbidity than individuals with a gradual onset. The Pearson’s chi-squared test of independence revealed that the percentage of participants who endorsed at least one lifetime

psychiatric diagnosis did not differ by onset group, $\chi^2(1, N = 181) = .42, p = .52$ (see Table 1).

For Hypothesis V, it was predicted that individuals with a sudden ME and CFS onset will evidence lower physical and role physical functioning than individuals with a gradual onset. A multivariate analysis of variance (MANOVA) was used to examine whether sudden onset mean scores on the Physical Functioning and Role Physical sub-scales of the SF-36 are significantly lower than gradual onset mean scores. There was not a significant effect of onset group on mental health functioning, $F(2, 180) = 1.33, p = .26$ (see Table 2 for means and standard deviations by onset group)

Table 1

Participants with Sudden Versus Gradual Onset Endorsing Viral Onset, Physical Illness Attribution, and At Least One Lifetime Psychiatric Diagnosis (N=181)

DSQ Item	Sudden	Gradual	χ^2	<i>p</i>
	(n=98)	(n=83)		
	% (n)	% (n)		
Infectious Onset	73.5 (72)	66.3 (55)	1.11	.29
Physical Attribution	96.9 (93)	93.9 (77)	.91	.34
Lifetime Psychiatric Dx	39.8 (39)	44.6 (37)	.42	.52

Table 2

Means and Standard Deviations on SF-36 Subscales by Onset Group (N=181)

SF-36 Subscale	Sudden	Gradual
	(n=98)	(n=83)
	M (SD)	M (SD)
Mental Health Functioning	74.35 (15.94)	68.80 (17.18)
Role Emotional	84.35 (33.57)	75.10 (39.93)
Physical Functioning	27.56 (18.56)	31.94 (18.03)
Role Physical	4.08 (14.22)	5.79 (16.33)

Phase Two

Qualitative analyses were employed in order to investigate how individuals with ME and CFS describe their illness onset, specifically with regard to the early days, weeks, or months in which their illness emerged. Intercoder reliability across two coders (the PI and an undergraduate level research assistant) was calculated on three randomly selected transcripts using the qualitative data analysis software program NVivo 10.0 (QSR International, 2012). After utilizing the three-stage method of establishing intercoder reliability and agreement as described by Campbell et al. (2013), the overall intercoder reliability was found to be excellent, with an average overall Kappa of 0.98 across the three coded

transcripts.

A summary of themes can be found in Tables 3 and 4. Each theme's meaning as it relates to the way in which participants described the onset and development of their illness is discussed below. The broad themes found in the analysis are as follows: onset/illness progression, illness cause, adapting and coping, hardworking, active lives prior to onset, healthy prior to onset, health problems prior to onset, comorbid health conditions, emotional response to onset, exertional effects, life limiting, stress, traumatic experiences, lack of support, support, and treatment limitations. The majority of themes include more specific subthemes and they are described in detail below. Whenever a direct quote is used from a participant, the unique participant number (1 through 14) is attributed to that person as well as the period of time in which their illness developed (as reported on the DSQ onset duration item). The DSQ onset period is shown in parentheses directly following the participant's number.

Onset/Illness Progression. Fourteen study participants described the period of time in which they first became ill. Different subthemes emerged within this larger theme of illness onset/illness progression. Descriptions of onset and illness progression were often described in conjunction with one another, and thus, they comprise one superordinate theme. Below are the various subordinate themes that emerged from the larger onset/illness progression category. Notably, many participants were included in more than one category.

Sudden. Seven participants described the onset of their illness as occurring suddenly and they used words such as “sudden,” “suddenly,” “rapidly,”

“overnight,” and “immediately.” A sudden illness onset was described by individuals who endorsed a range of onset periods on the DSQ including: 24 hours (n=2), over 1 week (n=2), over one month (n=1), over 2-6 months (n=1), and over 3 or more years (n=1).

Participant 4 (onset over 1 week) stated: “It was like something has suddenly happened.”

Flipping a light switch. Two of the seven participants within the “sudden” category used the analogy of flipping a light switch to describe the experience of their sudden onset. For example, participant 11 (onset over 3 or more years) stated, “it was a sudden onset” and “so it really was like someone had flipped a light switch and made me sick and never switched it off.”

Time. Three of the seven participants described their sudden onset in the context of time. Participant 3 (onset over 24 hours) stated: “my CFS came on suddenly” and “you know, it seemed overnight to me.”

Participant 5 (onset over 1 month) described how her illness began suddenly following a case of gastroenteritis. She stated, “suddenly, in November, I had, this um, in a week's time, I had this gastroenteritis. The initial insult was a few days. I started feeling the gastroenteritis, you know, within a week I had to go to the ER.”

Participant 10 (onset over 2-6 months) perceived her sudden onset as developing over a slightly longer time period than participant 5, stating, “very rapidly, over the series of like 2 months! Maybe 2 months at the most. I was normal and then I was sick.”

Exact date. Three participants were able to report the exact date of their illness onset. When asked about the period of time her first symptoms developed, Participant 3 (onset over 24 hours) stated, “It was April 29th, 2003.”

Definitive turning point/downturn. Five individuals described a definitive turning point/downturn during the period of time that their illness developed. This was often described as a point in the illness development when their health and functioning took a clear turn for the worse and symptoms became significantly more severe and debilitating. A definitive turning point was described by individuals who endorsed an onset period of one week (n=1), 7-12 months (n=2), and 1-2 years (n=2) on the DSQ.

For Participant 1 (onset over 7-12 months), her “definitive turning point/downturn” was the day that she also identifies as her illness onset. She used the exact phrase “definitive turning point,” stating, “there is a definitive turning point August 22nd, 2006. After that, my life was never the same.” She elaborated further stating “after that one [illness episode] I did not recover. I never returned to work. Yeah, so everything changed from that point on.”

Tipping point. Two participants described the theme in terms of a tipping point. For example, Participant 12 (onset over 7-12 months) stated “whatever happened in March, I had an infection or whatever it was, just kind of tipped me over the edge.”

Participant 13 (onset over 1-2 years) describes a series of infections and a colonoscopy as the tipping point of her illness stating, “2006 was sort of when the

sinus infections and all those infections started. And then 2008 was when I had my colonoscopy and it just kind of pushed me over the edge.”

Realization that something is wrong: Seven participants described a moment or period of time in which they understood that their illness was more than an ordinary sickness such as the flu, and there was something seriously wrong with them medically. A realization that something was wrong was described by individuals who endorsed a range of onset periods on the DSQ including: 24 hours (n=1), over 1 week (n=1), over one month (n=1), over 2-6 months (n=2), over 7-12 months (n=1), and over 1-2 years (n=1).

Participant 3 (onset over 24 hours) stated “I thought there was something seriously wrong with me and was sure that the blood tests would come up with some horrible news.”

Participant 6 (onset over 1 month) stated, “the notion that there was something seriously wrong started creeping in.”

Participant 1 (onset over 7-12 months) reported that she knew something was seriously wrong with her in the early stage of her illness stating,

It was in the first two weeks actually. Week one, after a week of cold you think it would get better. You know what getting better feels like, and it just wasn't happening. When I went into the second week, I was thinking, this is not normal, this is not normal.

Steady progression. Six participants described their illness as a steady progression in which the illness and accompanying symptoms accumulated and worsened over time. A steady illness progression was described by individuals

who endorsed a range of onset periods on the DSQ including: over 1 week (n=2), over one month (n=2), over 2-6 months (n=1), and over 1-2 years (n=1).

This theme is conveyed in a quote from Participant 6 (onset over 1 month) who described his illness progression in terms of a slow decline, stating “I had this initial hit and then there's just been this constant chipping away.” He also used the exact phrase “steady progression” stating, “from the initial illness it was this steady progression and I'd say it's been an accelerating one as of the last six or eight years have gone.”

Participant 4 (onset over 1 week) stated, “I was getting progressively worse.”

When referring to symptoms related to her illness Participant 14 (onset over 1 week) stated, “all these things were increasing over the following years.”

Wax and wane/illness episodes. When describing the period of time in which initial symptoms developed, nine participants described their illness as something that waxed and waned. They often described this experience in terms of “phases” “cycles” and “illness episodes.” These illness periods were more or less severe at times during the development of the illness. A wax and wane/illness episode onset pattern was described by individuals who endorsed a range of onset periods on the DSQ including: 24 hours (n=1), over 1 week (n=2), over one month (n=1), over 2-6 months (n=2), over 7-12 months (n=1), and over 1-2 years (n=2).

Participant 7 (onset over 2-6 months) provided a quote that specifically included the phrase “wax and wane.”

It was kind of uh... wax and wane. Uh...again, it would maybe last a week or two...after the birth of my son. I...I didn't feel good for four months. And after the birth of my daughter it took about three months.

Cycles. Two participants described this theme as “cycles” or “cyclical.”

When describing her illness cycles, Participant 1 (onset over 7-12 months) stated, “they would last for hours and hours and hours, and day after day after day... [they] would come in cycles.”

Participant 14 (onset over 1 week) described her illness cycles as variable in nature, stating, “eventually it went away and it would come back but it wasn't constant.”

Improvement. A sub-theme within the larger category of wax and wane was the specific description of periods in which illness improvement was noted. Six participants described periods of improvement with regard to their illness progression; however, this improvement was cyclical and always temporary. Periods of improvement may have been signified by either a brief or long period of symptom resolution, or a reduction in symptom severity. Participant 4 (onset over 1 week) stated, “I would start to get better and then by mid summer I would be feeling really pretty good. So the first year when this happened, I was...I thought you know, ok, you know I've gotten better.”

Long-term improvement. Only one participant described a “slow” improvement of her illness over time; therefore, it is not considered a theme within the data, rather a category that separates this participant from the others.

Participant 9 (onset over 24 hours) described how her illness has been slowly improving since 1986.

Well you know I got somewhat better over the years. I mean, obviously, it's been since '86, so there have been periods where I'm somewhat, but I'm certainly better than I was then, but um it's never you know gotten... really gotten better.

Unnoticed progression. Two participants indicated that their illness progression was unnoticed at first and that it was only years later, and in hindsight that they realized that their illness had been developing for a long period of time.

This theme was conveyed by Participant 6, (onset over 1 month), who now believes his illness started in his teen years. He reported that as a teen he did not have as much energy as other male peers his age; however, because of the large amount of energy that adolescent males have, he did not realize anything was wrong.

I was able to do everything else and that energy that I had lost [from the illness], knocked off a piece of you know of the vast amount [of energy] a 15 year old has, so it wasn't necessarily noticed. It was, you know, as such... It's really only in hindsight that I've realized, you know how significant it was at the time and how it would, how it would progress.

Participant 2 (onset over 1-2 years) described how she initially perceived her illness as part of the normal aging process. She stated:

It took me ages to realize, because at that stage I said maybe this is what getting old is about, because I'm 60 this year, you know, so at 57, I thought maybe this is the way life is just gonna be, you know what I mean?

Illness cause. Thirteen participants described their perceived cause of illness. Participant 12 (onset over 7-12 months) was the only participant who did not describe a perceived cause of illness. Subordinate themes within the larger theme of illness cause are listed below. It is important to note that many individuals reported that there was more than one possible cause of their illness, and therefore, they are included within more than one sub-theme. Three sub-themes emerged from the larger theme of illness cause: 1. infectious/viral, 2. immune component, and 3. stress as a precursor. Other causes also emerged from the data but were not considered themes, as they were endorsed by one person. The additional illness causes described include the belief that the illness was caused by an adrenal problem, autonomic problems, diet, mosquito pesticides, mitochondrial disease, mold, and physical trauma.

Infectious/viral. One sub-theme that emerged within the larger category of illness cause was the belief that the illness was caused by a virus or an infectious agent. Thirteen individuals reported that the cause or partial cause of their illness was viral or infectious in nature.

When describing the onset period of her illness, Participant 4 (over 1 week) stated “I had something that felt to me like a cold, or you know, a virus, it felt to me like a virus.”

Mono/Epstein-Barr virus (EBV). Six participants specifically believed that the development of mono and/or the Epstein-Barr virus (EBV) was the cause or the partial cause of their illness. For example, this sub-theme was conveyed by Participant 6 (over 1 month) who stated, “I got mono and never fully recovered.”

Immune component. Five participants specifically described an immune component to their illness onset, development, and/or progression.

Participant 11 (onset over 3 or more years) stated, “when you got mono on top of carrying Lyme, which is affecting the immune system, of course you're never going to get better.”

Participant 13 (over 1-2 years) stated:

I do think that like uh... a series of illnesses, like stuff growing up sort of contributed and I just...I guess I just want to mention, I had um mono, which was in the mid 90's. I had bronchitis in college and the late 90's, I was in a bad car accident in 2000... um, so I did have like a couple other significant things that I...I personally think weakened my [immune] system a little bit each time along the way.

Stress as a precursor. While the majority of participants discussed stressful events leading up to or following their illness onset, two participants believed that stress played a significant role in the development of their illness. Participant 2 (onset over 1-2 years) stated, “so I think you know I keep looking for precursor things. I think that you've gotta add stress to the possible things.”

When describing the cause of her illness development, Participant 5 (over 1 month) stated, “it was probably overworking and the stress of moving.”

Adapting and Coping. Nine participants described ways in which they coped and adapted to their illness onset. Adaptations and coping strategies in response to the illness were described by individuals who endorsed a range of onset periods on the DSQ including: 24 hours (n=1), over 1 week (n=2), over one month (n=1), over 2-6 months (n=2), over 7-12 months (n=1), over 1-2 years (n=1), and over 3 or more years (n=1).

Behavioral coping. Within this larger theme, eight participants described behavioral forms of coping such as pacing, reducing work hours, reducing social activities, attending support groups, and creating symptom lists to keep track of the illness progression.

Participant 2 (over 1-2 years) discussed the benefits of pacing stating:

Two years in [to the illness] I attended a multidisciplinary chronic pain program which was eight hours a day for a month, and that was sort of enormously helpful in helping me come to terms with the fact that I couldn't do stuff, and in working out what my limits were and what I could do about it, and I think as a result of that program, I was able to sorta work more effectively, and I ended up getting tenure... and I think it's as clear as that. Without that program I think I probably would not have got tenure.

Participant 1 (over 7-12 months) discussed how she adapted by changing her daily routine to accommodate the illness. She stated, “I had to learn to

schedule to take a shower, and have at least two hours before getting up and doing something else. I needed to rest just to take a shower.”

Change in mindset. Four participants discussed adapting to or coping with the illness by using internal and cognitive strategies, such as engaging in mindfulness/meditation, adopting a philosophical sense of acceptance of the illness, and optimistic thinking.

This theme is conveyed in a quote by Participant 2 (onset over 1-2 years) who discussed the benefits of mindfulness and meditation as forms of coping. She stated:

Meditation, where you also watch your thoughts and try to be detached about them...and the very day I was diagnosed happened to be a day for that. I found that ability to be a bit detached just enormously helpful and it has continued to be a huge coping strategy.

Participant 8 (onset over 3 or more years) discussed the value of acceptance of her illness stating, “I accepted it pretty philosophically. I didn't do a lot of chest beating.”

Hardworking. Nine participants described themselves as hardworking or overworking in the year leading up to their illness onset and/or during the early development of their illness. Individuals who described working hard in the year leading up to their illness onset or during the early development of their illness endorsed a range of onset periods on the DSQ including: 24 hours (n=1), over 1

week (n=2), over one month (n=2), over 2-6 months (n=1), over 1-2 years (n=2), and over 3 or more years (n=1).

Two participants specifically used the term “overworking.” For example, Participant 3 (onset over 24 hours) stated, “at the time I was a single mom with two teenagers and a mortgage. I worked full time. I loved my job um but I was indeed overworking for sure.”

Participant 6 (onset over 1 month) discussed the price he paid for working too hard at the time that his illness was developing.

I think that I worked longer than I should have, um for my health, for sure... um but I think I pushed myself you know a lot further than I think a lot of people might. Um which just kinda made my decline that much worse um you know and so I've had loss of function since then.

Active prior to onset. All 14 participants described having active lifestyles prior to the onset of their illness. They described their engagement in sports, social activities, and work related activities.

When describing the year prior to her illness onset, Participant 1 (onset over 7-12 months) stated, “it was great, I did yoga, belly dancing, meditation, you know all sorts of things. I was finishing my bachelors degree in psychology.”

Participant 5 (onset over 1 month) described her many physical activities prior to her illness onset. She stated, “I was an avid hiker and climber and biker”

Participant 7 (onset over 2-6 months) described her active lifestyle with fondness stating, “I was working as a nurse full time during those times, and felt pretty

good. And was active in helping my brother take care of their kids, and going on day trips and then dating um...and just enjoying life.”

Healthy prior to onset. Nine participants considered themselves healthy prior to their illness onset. Many of these participants also identified health conditions or problems prior to their illness development; however, they still considered themselves as relatively healthy individuals. Individuals who described themselves as healthy prior to onset endorsed a range of onset periods on the DSQ including: 24 hours (n=2), over 1 week (n=1), over one month (n=2), over 7-12 months (n=1), over 1-2 years (n=1), and over 3 or more years (n=2).

Participant 11 (onset over 3 or more years) discussed her health prior to onset stating, “I was in the best shape of my life.”

Health problems prior to onset. While the majority of participants described themselves as relatively healthy prior to the onset of their illness, many of these same participants identified health problems and ailments in the months or year leading up to the onset of the illness. Eleven participants described one or more health problems leading up to their illness onset. Participants who described themselves as having health problems prior to onset endorsed a range of onset periods on the DSQ including: 24 hours (n=2), over 1 week (n=1), over one month (n=1), over 2-6 months (n=2), over 7-12 months (n=1), over 1-2 years (n=2), and over 3 or more years (n=2). For example, Participant 1 (onset over 7-12 months) described health symptoms she experienced in the months leading up to her illness.

I also noticed that kind of fatigue, and uh being much more tired than usual.... I noticed that. And then in the summer, July of 2006, July, August, I started noticing that when I stood for ten to fifteen minutes I would get out of breath and I would almost faint, I would have to sit down, it was so extreme I would break out into this sweat. I would feel extremely weak. I would need to sit down. That was very unusual but that definitely started happening around July, August.

Frequent sicknesses. Five participants described experiencing frequent sicknesses, such as colds or persistent strep throat prior to their illness onset.

Participant 7 (onset over 2-6 months) described a series of sicknesses while she was studying in nursing school and prior to the development of her illness.

I recall that I was sick a lot in nursing school but it seemed to be more viruses because I had not been exposed, especially when I was in pediatrics. I was like sick all the time. I was hospitalized with pneumonia...um, but again, I thought I was just...that was just my resistance building up. I had several episodes of strep throat.

Participant 5 (onset over 1 month) also described frequent sicknesses in the year leading up to her illness onset.

Prior to that I'd been having, maybe, well, I would say, everybody seems to...I'm not alone, I think in everybody saying that maybe the year or year or two prior in hindsight you seem to have a little

bit more um problems then you normally would, um you know, like flus or things that you didn't have before.

Comorbid health conditions. Eleven participants reported that they had comorbid health conditions during their ME and CFS progression. Three subordinate themes emerged from the data: 1. fibromyalgia, 2. postural orthostatic tachycardia (POTS), and 3. irritable bowel syndrome (IBS). Additional comorbidities were reported; however they were not included as themes as only one participant endorsed having each condition. These comorbidities included migraines, temporomandibular disorders (TMD/TMJ), multiple chemical sensitivities, Lyme disease, thyroiditis, degenerative eye disease, ulcers, asthma, and deep vein thrombosis. Individuals who described comorbid health problems endorsed a range of onset periods on the DSQ including: 24 hours (n=1), over 1 week (n=2), over one month (n=2), over 2-6 months (n=1), over 7-12 months (n=1), over 1-2 years (n=2), and over 3 or more years (n=2).

Fibromyalgia. Six participants reported that they had a diagnosis of fibromyalgia in addition to ME/CFS.

Participant 4 (onset over 1 week) discussed how when she was diagnosed with fibromyalgia she was not surprised, as she had wondered since she was a teenager if she had the condition.

I also saw a rheumatologist who thought I had fibromyalgia and I kind of dismissed the diagnosis, because I thought I had fibromyalgia but I thought I had fibromyalgia you know, ever since I was a teenager...and I mean it wasn't diagnosed then, but

when I first...when I first came...when I first learned what it was, which was several years prior to this time, I thought I probably had fibromyalgia, but I didn't think it was a big deal, but it didn't stop me from doing anything.

Postural orthostatic tachycardia. Three participants reported that they experienced Postural Orthostatic Tachycardia (POTS). Participant 6 (onset over 1 month) described how he was initially diagnosed with activity induced asthma when he was younger, but later realized he has been suffering from POTS all along. He stated, “the only diagnosis I got at the time was um activity induced asthma, and I think that, what was really going on was POTS, but nobody...POTS wasn't even in the lexicon in 1980. Nobody looked for that.”

Irritable bowel syndrome. Two participants reported that they had irritable bowel syndrome (IBS). Participant 13 (onset over 1-2 years) described how she was diagnosed with multiple conditions including IBS stating, “I was diagnosed with IBS, TMJ, migraines, chronic fatigue syndrome, and fibromyalgia.”

Emotional Response to Onset. Nine participants described their emotional response to their illness onset. A range of responses were noted, including fear, depression, confusion, and anger. Individuals who described an emotional response to onset endorsed a range of onset periods on the DSQ including: 24 hours (n=1), over 1 week (n=2), over one month (n=1), over 2-6 months (n=2), over 1-2 years (n=1), and over 3 or more years (n=2).

Fear. Two participants described the feeling of fear in response to their illness onset. Participant 2 (onset over 1-2 years) described telling her family that she would never recover. She stated:

I'm calling up one of my sisters...my family is in Australia, so is my husband, and telling her about how scared I was that I wouldn't get well and I'd have to give up my job. I remember being just very, very freaked about the possibility that I had this disease that wouldn't go away.

Depression/sadness. Four participants described experiencing periods of depression following the onset of their illness. Many participants described how the depression came once they came to the realization that the illness may never resolve.

Participant 10 (onset over 2-6 months) described how the depression hit a year after her illness onset. She stated: Then after about a year, I'm starting to realize that this might not go away. This might take a while to go away. And I just started getting really depressed." She elaborated further stating, "It was just like, this is insane, and you start to get really depressed.

She also described the belief that her depression was not wholly psychological. She suggested that the depression was partly a physiological response to her illness and partly due to environmental reasons such as invalidation from others.

It really lingered. I mean it's been up and down for the past 25 years of the depression, and I think part of it is physiological. I

think there is something about the illness that pushes people into the depression, and then I also think that it's environmental, you know. I think that when your life has been limited in such a way and your not being validated as someone who has an illness that's a very depressive situation.

Confused. Two participants described the feeling of confusion in response to their illness onset. Participant 11 (onset over 3 or more years) described feeling “perplexed” about how she could become sick in a matter of a day. She stated, “so a lot of it was denial, um, but you know just being totally perplexed by how you could go from totally healthy one day to being totally sick the next and not even know what happened.”

Angry. Two participants described feeling angry during their illness onset. Participant 10 (onset over 2-6 months) described anger about getting negative feedback from her doctors and their inability to tell her how to treat her illness. She stated, “I was getting angry! I was like don't tell me that I'm crazy, just tell me what I need to do.”

No emotional impact. Two participants reported that their illness onset and early progression did not significantly impact them emotionally. Participant 11 (onset over 3 or more years) stated, “Mentally, I was still emotionally there.”

Exertional Effects. Eleven participants described how exertion, whether physical or mental, triggered or worsened their symptoms. Mild to severe exertion was described as causing a further decline in health. Individuals who described an exertional effects endorsed a range of onset periods on the DSQ including: 24

hours (n=1), over 1 week (n=2), over one month (n=2), over 2-6 months (n=1), over 7-12 months (n=2), over 1-2 years (n=2), and over 3 or more years (n=1).

Participant 4 (onset over 1 week) described the difficulty of going to the grocery store. She stated, “It wouldn’t be uncommon for me to go to the grocery store and have to rest in the car for about 20 minutes before I would go in and doing grocery shopping.”

Participant 6 (onset over 1 month) described the impact that mental exertion had on his illness. He described an instance in which he had severe exertional effects following the completion of a neuropsychological evaluation for his disability assessment. He stated:

I had to do an interview for disability, a neuropsych evaluation... an all day thing... um and I was in bed for three weeks. I was in horrible shape after that. I was essentially sitting at a desk for 8 hours.

Life Limiting. Twelve participants described how the illness limited their lives during their illness onset. They also discussed how the illness continues to limit their lives. Participants described ways in which their family, social, and work lives were negatively affected by the illness. They also discussed a decline in their functional abilities. Individuals who described exertional effects endorsed a range of onset periods on the DSQ including: 24 hours (n=2), over 1 week (n=2), over one month (n=2), over 2-6 months (n=1), over 7-12 months (n=1), over 1-2 years (n=2), and over 3 or more years (n=2).

Participant 3 (onset over 24 hours) described the negative impact the illness had on her family and on her social life.

I was pretty much unable to take care of my kids and work at the same time, so between coming home and just dropping at the door... um my kids were old enough to sorta help out, and uh they would sorta throw together some sorta of a dinner and we would have dinner together but I couldn't really socialize. I was so dead by the end of the day, I was just like a plasma, and that went on again I guess until about October, so I was sleeping at every coffee break lunch break, I was going home and going straight to bed, um I wasn't eating well, my kids weren't eating well.

Participant 6 (over 1 month) specifically used the term "life limiting" and he described how he eventually became so limited that he could not drive and was mostly confined to his bed. He stated, "I got to the point where going to the doctor and then dropping off prescriptions off at a pharmacy was a limit, and I'm not driving basically... not driving at all right now, and you know mostly bed bound."

Stress. Twelve participants described experiencing stress in the year leading up and/or following their illness onset. Individuals who described stressful events or experiences endorsed a range of onset periods on the DSQ including: 24 hours (n=1), over 1 week (n=2), over one month (n=2), over 2-6 months (n=2), over 7-12 months (n=2), over 1-2 years (n=2), and over 3 or more years (n=1).

Participant 5 (onset over 1 month) described multiple stressors leading up to her illness onset, including negotiating to buy a house with her husband, participating in a big art show, and the sudden death of her mother.

When we first moved, since it was pretty stressful doing all the negotiating to get the house, stuff like that. It was at also at the same time, that we had our biggest art show of the year that we had to do, the resorts festival, so we were getting ready to do a seventeen day sting there at the same time that we were closing on our house, um so it was all that going on... I also had uh oh, oh, geez, I almost forgot, April my mother died suddenly um, how could I forget that...um we weren't terribly close but she was my mom, and we had a big family.

Participant 11 (onset over 3 or more years) described the stress she was experiencing concurrently with the onset of her illness. Specifically she discusses the stressors she experienced during her basic training to be an air force pilot.

Unfortunately it happened on the second day of four weeks of basic training and I had no clue what had gone on other than you know it was a very stressful time. I was uh, I had to do very well at basic training because at the time, the pilot slots for women were very uh rare, and so you had to do very well on your application in order to get selected, and a lot of personal pressure on me, and then that first night, of course they overload on purpose because they are trying to make you quit and um, I stayed up all night, pulled an

all nighter essentially because your socks had to be exactly such and such length, and you know, all the certain way and all of that and they had you go to meetings and all this other stuff during the first day that you never had a chance to put this together.

Traumatic experiences. Five individuals reported that they experienced trauma prior to the onset of their illness. The traumatic experiences that were discussed included a car accident, rape, falling down a staircase, severe childhood burns, and the traumatic delivery of one of their children. Three out of the five participants experienced the trauma as adults and closer in time to the onset of their illness. Individuals who described traumatic experiences endorsed the following onset periods on the DSQ: 24 hours (n=1), over 2-6 months (n=1), over 7-12 months (n=1), over 1-2 years (n=1), and over 3 or more years (n=1).

Participant 3 (onset over 24 hours) suggested that the physical trauma she experienced after falling down stairs had a role in her illness development.

December 2002, I had a fall, um I fell down some stairs and was knocked out, so that was... you know, often you'll hear about people who got fibromyalgia, they say that it can happen after some sort of traumatic event, physical event or emotional event, so I wonder if that played a part of it.

Participant 13 (onset over 1-2 years) described a car accident she experienced prior to her illness development.

Yeah, so I um...I guess the most recent thing before all of the um...the...sinus infections and stuff was a car accident in 2000.

Where I was rear-ended and I got very bad whiplash, and it took a long time to get over that. I'm...my neck is still not the same. It still gets really tight. I developed scar tissue and stuff, so it was pretty significant for me.

This participant also suggested that the car accident along with a “series of illnesses” weakened her immune system.

I had um mono, which was in the mid '90's. I had bronchitis in college and the late '90's. I was in a bad car accident in 2000. Um, so I did have like a couple other significant things that I...I personally think weakened my system a little bit each time along the way.

Lack of support. Seven participants described a lack of support following the onset of their illness. This included a lack of support from family, friends, and physicians. Individuals who described a lack of support following their illness onset endorsed a range of onset periods on the DSQ including: 24 hours (n=1), over 1 week (n=1), over one month (n=2), over 2-6 months (n=1), over 1-2 years (n=1), and over 3 or more years (n=1).

Participant 10 (onset over 2-6 months) describes the lack of support she received from her family, friends, and her boyfriend during the onset of her illness. She stated:

you're alone, usually, right! You're... you're completely alone right? I did not have a support system. My parents are not supportive people. My boyfriend was not a supportive person!

(laughs) so I did not have support to encourage me... that... you know, maybe you can get over this. You know, maybe life will get better. That didn't happen, you know. I was alone most of the time. I was just trying to figure things out and then not getting a lot of help from the world.

Participant 5 (onset over 1 month) described the lack of support she received from doctors. She stated, "I kinda toughed it out on my own, because my past experiences with doctors, including the gastro I did see in December, kinda just blew me off."

Support. Three participants described the support that they received during the onset and early progression of their illness. Individuals who described support following their illness onset endorsed the following onset periods on the DSQ including: over one month (n=1) and over 1-2 years (n=2).

Participant 2 (onset over 1-2 years) described the significant support that she received from her primary care physician during the period of time that she became ill.

I consulted my own primary care physician who is someone who always believes me when I tell her how I'm feeling. She's great. She didn't blow me away which is I think the important thing. I think that I sort of totally proved myself as being a good dooby before I got sick because nobody thought I was faking and they have been incredibly understanding.

Participant 6 (onset over 1 month) described the support he received from his general practitioner. He stated, “I guess I have to say, you know, as far as the way some people get treated by doctor's, I've been lucky. My GP has been very supportive. He also described the support he received from his wife stating, “my wife, you know cooks and cleans and takes care of the kids, and I do what I can for moral support essentially.”

Treatment limitations. Six participants described limitations of the treatments that they were receiving during the period of time when they became ill. Individuals who described treatment limitations endorsed a range of onset periods on the DSQ including: 24 hours (n=1), over 1 week (n=1), over one month (n=2), and over 1-2 years (n=2).

Participant 5 (onset over 1 month) described how her doctor told her that she could exercise, which only worsened her condition. She described how she learned later on that exercise could worsen her prognosis.

Exercising and activity after the onset of illness to worsen your prognosis so... I read that too late (laughs) and my doctors told me that I had CFS which you are allowed to exercise... and if they had known about any of ...they would have said hey, cut this out, lay down.

Participant 6 (onset over 1 month) described the antiviral treatment his doctor has tried. He stated, “she’s done you know antivirals and other things and we haven’t had any real luck. Basically getting treatment is either helping symptoms a little bit or it doesn’t help.”

Symptoms. All fourteen participants identified symptoms that were experienced during the onset of their illness. Symptoms primarily fell in the following broad categories: flu-like symptoms, digestive symptoms, pain symptoms, autonomic symptoms, fatigue, post exertional malaise (PEM), sleep difficulties, and cognitive impairment. See Tables 5 and 6 for the full list of symptoms, including total frequency and percentage.

Timeline Graphs

A total of 14 illness timeline graphs were constructed based on the participant interviews completed for the qualitative portion of the study. Seven participants (50 %) have provided corrections and feedback on their illness timelines and their graphs can be found in Appendix C. The illness timeline graphs provided a detailed chronology of each individual's functioning over the course of their illness including the year(s) leading up to the onset and the initial month(s) and year(s) of onset. The illness timeline graphs reveal periods of severe disability, remission, and fluctuating illness patterns in a biographical context. The graphs are presented in Appendix C in order of the period of time in which individuals reported on the DSQ that their illness developed (24 hours, over 1 week over 1 month, over 2-6 months, over 7-12 months, over 1-2 years, over 3 or more years). Areas shaded in green signify functioning levels above 50 and areas shaded in red signify functioning levels below 50.

Participant Impressions

Feedback and impressions have been shared by eight out of the 14 participants interviewed for phase two of the study. Overall, the feedback has

been positive and all participants have indicated that the themes and illness timeline graphs effectively summarize their experience. Five out of the eight participants provided minor corrections and additions to their illness graphs. Three reported that their graphs did not require any corrections/changes. After reviewing the overall themes and key quotes that conveyed each theme, one participant commented, “I found that I could relate to the other participants as well. Each quote might as well have come from me too.” Two participants elaborated on some themes. One participant who had described stress as a partial precursor for her illness development elaborated on this theme by describing how her stress was “good stress” that involved positive milestones in life (e.g. raising children and buying a house). She stated “I was having the time of my life.” Another participant commented on the exertional effects theme and described how many individuals with the illness “realize too late the benefits of pacing.” She discussed how participants often realize the importance of reducing activities after the exertional effects have already taken a severe toll on the body. One participant noticed that she was initially categorized in the “onset over 3 or more years” onset group based on her answer to the onset question on the DSQ. However, she stated that her illness was sudden and developed over one day. This was reflected in her qualitative interview as well. A few participants described an emotional reaction to reading the overall themes and from receiving their illness timeline graphs. One participant stated, “reading through my narrative made me very emotional. There is something about looking at your own words that makes it very validating. With that, comes an incredibly strong and direct connection to

the suffering I am having to minimize each and every day. It's like the floodgates open, and it's hard to contain all the emotions that are normally tucked away.”

Table 3

Themes Pertaining to Onset/Progression, Illness Cause, Coping, Work, and Health (N=14)

Themes	Total % (n)
Onset/Illness Progression	100 (14)
Sudden	50 (7)
Exact Date	21 (3)
Definitive Turning Point	36 (5)
Realization that Something is Wrong	50 (7)
Steady Progression	43 (6)
Wax and Wane	64 (9)
Unnoticed Progression	14 (2)
Illness Cause	93 (13)
Viral	93 (13)
Mono/EBV	43 (6)
Immune	36 (5)
Stress	14 (2)
Adapting and Coping	64 (9)
Behavioral Coping	57 (8)
Change in Mindset	29 (4)
Hardworking	64 (9)
Active Prior to Onset	100 (14)
Healthy Prior to Onset	64 (9)
Health Problems to Onset	79 (11)
Frequent Sickneses	36 (5)
Comorbid Health Conditions	71 (10)
Fibromyalgia	43 (6)
POTS	21 (3)
IBS	14 (2)

Table 4

Themes Pertaining to Emotional Health, Exertion, Limitations, Stressors, and Treatment Limitations (N=14)

Themes	Total % (n)
Emotional Response to Onset	64 (9)
Fear	14 (2)
Depression	21 (3)
Confusion	14 (2)
Anger	14 (2)
No emotional response	14 (2)
Exertional Effects	79 (11)
Life Limiting	86 (12)
Stress	86 (12)
Traumatic Experience	36 (5)
Lack of Support	50 (7)
Support	21 (3)
Treatment Limitations	43 (6)

Table 5

Frequency of Flu-like, Gastrointestinal, Pain, and Autonomic Symptoms at Onset (N=14)

Symptoms	Total % (n)
Flu-like	14 (2)
Chills	7 (1)
Sweating	7 (1)
Sore throat	7 (1)
Fever	29 (4)
Headaches	36 (5)
Coughing	7 (1)
Vomiting	7 (1)
Swollen Lymph Nodes/Glands	21 (3)
Irritable Bowel Symptoms	14 (2)
Nausea	14 (2)
Diarrhea	21 (3)
Pain	36 (5)
Stomach Pain	21 (3)
Muscle Pain	14 (2)
Joint Pain	14 (2)
Inflammation	7 (1)
Cramping	14 (2)
Heart Pain	7 (1)
Autonomic	7 (1)
Heart Rate Increase	14 (2)
Irregular Heart Beat	7 (1)
Low Blood Pressure	7 (1)
Dizziness	7 (1)

Table 6

Frequency of Fatigue, Sleep Difficulties, Cognitive Difficulties, Sensitivities, Endocrine, and Miscellaneous Symptoms at Onset (N=14)

Symptoms	Total % (n)
Fatigue	21 (3)
Tired	21 (3)
Exhaustion	57 (8)
No Energy	21 (3)
Post Exertional Malaise	21 (3)
Dead Weight	7 (1)
Insomnia	21 (3)
Lack Sleep	21 (3)
Unrefreshing Sleep	14 (2)
Nighttime Awakenings	7 (1)
Increased Sleep	21 (3)
Cognitive Difficulties	43 (6)
Multitasking Difficulties	7 (1)
Brain fog	7 (1)
Difficultly Focusing	7 (1)
Noise Sensitivity	7 (1)
Light Sensitivity	21 (3)
Weak feeling	14 (2)
Eye Twitching	7 (1)
Difficulty Swallowing	7 (1)
Weight loss	7 (1)
Numbness	14 (2)
Temperature Intolerance	14 (2)
Tingling	7 (1)
Malaise	7 (1)
Breathing Difficulty	7 (1)
Visual Difficulty	7 (1)

Discussion

The current study serves as an investigation of onset patterns associated with ME and CFS. Overall, results of the quantitative portion of the study (phase one) revealed that mode of illness onset (sudden versus gradual) did not differentiate individuals on key factors related to etiology, psychopathology, and prognosis. The qualitative portion of the study (phase two) provided rich descriptions of onset experiences across participants who endorsed a range of onset timeframes on the DePaul Symptom Questionnaire (DSQ; from 24 hours to over 3 years). These rich descriptions provide insight into the symptoms, onset patterns, and early characteristics associated with the initial phase of the illness.

Quantitative/Phase One: Major Findings and Implications

Results of hypothesis I revealed that the proportion of participants who reported that an infection preceded illness onset did not significantly differ by mode of illness onset (sudden versus gradual). In the current study, more than half of participants in both onset groups endorsed an infectious cause of illness on the DePaul Symptom Questionnaire (DSQ; Jason et al., 2010). Previous research has suggested that a sudden/acute onset of CFS is associated with a viral/infectious etiology (Komaroff, 1988, 1994; Hay & Jenkins, 1994). The findings from the current study suggest that participants perceive the cause of their illness as infectious/viral regardless of onset type.

Results of hypothesis II revealed that the percentage of participants who reported the cause of their illness as “Definitely Physical” or “Mainly Physical” did not differ across individuals with a sudden versus gradual onset. Previous

studies have found that participants with CFS are significantly more likely to report that their illness developed from physical causes rather than psychological causes (Butler, J. A., Chalder, T., & Wessely, S., 2001; Clements, A., Sharpe, M., Simkin, S., Borrill, J., & Hawton, K., 1997; Powell, R., Dolan, R., & Wessely, S., 1990). To this author's knowledge, no previous studies have investigated whether participants' attributions (physical versus psychological) of the cause of ME and CFS is differentiated by mode of illness onset. Results of the current study were insignificant, revealing that illness attribution was not differentiated by mode of onset. This finding is consistent with the qualitative phase of the current study (presented below) showing that nearly all participants (93%) regardless of onset group attributed the cause or partial cause of their illness to an infection or virus.

Results of hypothesis III revealed that there was not a clinically significant main effect of onset group on mental health functioning; however, a trend was noted in the expected direction, with participants in the sudden onset group reporting higher mental health functioning than individuals in the gradual onset group. Furthermore, results of hypothesis IV revealed that the percentage of participants who endorsed at least one lifetime psychiatric diagnosis did not differ by onset group. Overall, these results suggest that mode of illness onset did not differentiate individuals on factors related to psychopathology. Findings within the ME and CFS literature are mixed with regard to whether illness onset can differentiate individuals based on psychological factors. Consistent with the current findings, Cukor, Tiersky, and Natelson (2000) did not find evidence that sudden versus gradual onset groups can be differentiated based on

psychopathology. Jason et al. (2000) and Reyes et al. (1999) found that individuals with a sudden onset of CFS from community-based samples evidenced higher rates of psychiatric comorbidity; whereas, DeLuca et al. (1997) found that those with a gradual onset evidenced higher rates of psychiatric comorbidity. Furthermore, Salit (1997) found fewer rates of depression in individuals with a sudden/acute onset.

Results of hypothesis V revealed that there was not a significant effect of onset group on overall physical functioning. Findings are mixed within the CFS literature regarding the extent to which illness onset is predictive of health outcomes. Jason et al. (2000) and Njoke, Jason, Porter, and Brown (2009) found that sudden illness onset was associated with poorer outcomes compared to those with a gradual onset. However, Reyes et al. (1999) and Hill et al. (1999) found that mode of illness onset was not predictive of health outcomes.

Overall, results of the quantitative findings, suggest that mode of illness onset as it has been defined in the literature (sudden versus gradual) and in the current study, may not significantly differentiate individuals on factors related to illness cause, psychopathology, and health outcomes in individuals with ME and CFS. Interestingly, a recent study by Jason, Evans, Brown, Sunnquist, and Newton (2015) found that participants who met criteria for ME with an acute onset (onset over 24 hours to 1 week) had greater physical function impairment as well as physical, mental, and cognitive problems than individuals who met CFS criteria. These findings suggest that the combination of mode of illness onset and case criteria may be important for identifying subtypes of the illness.

Qualitative/Phase Two: Major Findings and Implications

The qualitative interviews in the current study yielded rich descriptions that provide insight into the way people with ME and CFS describe their illness onset, including perceptions of mode of onset, illness progression, functional, social, and treatment limitations, emotional responses, degree of support from others, and early health problems and symptoms. Within the category of onset/illness progression, 50% of participants endorsed a sudden onset of ME and/or CFS. These findings are consistent with the qualitative study by Ray et al. (1998), which revealed that 50% of a sample of CFS participants reported a sudden illness onset. Another onset theme that emerged within the current study was the experience of a steady progression of symptoms that accumulated over time (endorsed by 43% of participants). This theme is also consistent with Ray et al. (1998) who found that 25% of their study population described a gradual illness onset in which people reported a slow, worsening of symptoms over time. A third theme that emerged within the onset/illness progression category of the current study was the experience of a wax and wane progression in which there were periods of improvement/remission and periods of worsening symptoms accompanied by a noticeable decline in functioning. This wax and wane pattern was described by 64% of participants, who used terms such as illness episodes, phases, and cycles. This theme is similar to the two-phase illness onset group previously described by Ray et al. (1998). Ray et al. (1998) describes this phased onset as a sharp deterioration of health followed by improvement in phase one, which is then followed by another deterioration of symptoms in phase two. Ray et

al. found this pattern in 23% of their sample. The wax and wane pattern found in the current study differs from the two-phase theme described by Ray et al. (1998), in that it is not limited to “two phases.” Many participants in the current study described numerous illness phases throughout the course of their illness progression. Another way in which the onset themes of the current study differ from Ray and colleagues (1998) is that they are not mutually exclusive. Specifically, some participants endorsed a sudden onset followed by a steady progression of the illness. Other participants described a sudden onset and a wax and wane illness course rather than a steady progression of symptoms.

Additional onset/illness progression themes emerged from the data. A subset (21%) of participants reported the exact date of illness onset. As might be expected, all of these individuals described their onset as sudden. DeLuca et al. (1998) suggested that a specific date is necessary in order to categorize someone as having a sudden CFS onset. However, the qualitative findings of the current study reveal that the majority of individuals who endorsed a sudden illness onset did not name the exact date of onset. This finding suggests that requiring a specific date of onset could be too strict for determining mode of illness onset.

A subset (14%) of participants described the experience of an unnoticed illness progression. These individuals also described a steady progression of their illness in which symptoms and functional limitations slowly increased over time. Previous qualitative studies have not specifically identified or described this experience of an unnoticed illness progression. These findings have clinical implications, as individuals who do not recognize the progression of their illness

until years later likely will not seek medical care and support as quickly as others who identify that something is wrong earlier in the illness development. This could ultimately impact the course, treatment, and prognosis of the illness.

Thirty six percent of participants also described a definitive turning point/downturn in their illness progression in which symptoms and functional limitations significantly worsened. Furthermore, 50% described a moment in the illness progression in which they realized that something was seriously and medically wrong with them. These experiences were significant for participants as they signified a period of the illness development in which there was gained insight on the seriousness of the illness. These experiences could have clinical significance for patients, as they potentially mark a point in time in which they feel the need to seek medical treatment and make steps to receive a diagnosis.

The majority of participants (93%) from the qualitative sample reported that a virus or infection was the cause of or partial cause of the ME or CFS onset. This finding is consistent with the quantitative findings in phase one that are presented above. The majority of participants from the larger quantitative sample reported on the DSQ that an infection or virus preceded the illness onset. Furthermore, mode of illness onset did not differentiate individuals based on viral/infectious etiology. These results are also consistent with Ray et al. (1998) who found that a subset of all three onset groups identified in their study (sudden, gradual, and phased) endorsed a viral/infectious onset.

Ray et al. (1998) found that a portion of participants attributed their illness development to their immune system “breaking down.” A subset (36%) of

participants in the current study also endorsed an immune component to their illness cause. These individuals typically described a series of infections (one individual described infections in combination with a physical trauma) that negatively impacted the immune system over time. These findings are consistent with an immune component theory posed by Hyde et al. (2007) who asserts that ME often follows multiple, minor infections in individuals with susceptible immune systems or immune systems that are weakened by severe stressors (e.g. contact with infectious persons, exhaustion, trauma, immunizations, epidemic disease, travel and exposure to virulent agents). Additionally, prior research has evidenced immune dysfunction and damage to the CNS in individuals with CFS (Broderick et al., 2010).

Ray et al. (1998) found that individuals with a sudden or “sharp” onset were most likely to report that an infection was a trigger for illness onset. Additionally, Ray reported that individuals with a sudden onset more often describe pre-onset factors (e.g. stress, overactivity, predispositions for health problems etc.) that may have built up and contributed to the onset of illness. Additionally, Ray found that individuals in the phased group were more likely to describe exacerbating illness factors that followed the onset of their illness. In contrast, the current study showed that the majority of participants identified an infection or virus as the trigger for their illness regardless of onset type. Furthermore, pre-onset triggers and post-onset exacerbating factors (e.g. overexertion) were endorsed regardless of onset type.

A small subset of participants (14%) reported that stress was a partial cause of their illness onset. Ray et al. (1998) found that some individuals in their sample described what Ray and colleagues referred to as “complex” onset contributory factors, which included a combination of infection, overexertion, and stress. A qualitative study of illness beliefs in individuals with CFS revealed that 56% of participants believed that stress/lifestyle contributed to the onset of CFS; however, similar to the current study, none believed that stress was the sole cause of illness onset (Clements et al. 1997). Salit found that individuals with CFS (regardless of onset group) reported a higher number of stressful life events prior to CFS onset compared to a control group (1997). In contrast MacDonald et al., (1996) did not find an increase in life stress in the year before the onset of CFS.

Thirty six percent of participants described traumatic events over the course of their lives. Only one participant suggested that the cause of the illness was partially due to the trauma. Overall, the current study revealed that the majority of participants (86%) endorsed stressors in the year leading up to and following illness onset; however, the stress was not described as a precursor to the development of the illness, but rather something that exacerbated the illness.

Many participants in the current study described the experience of working hard, and a small subset within this theme discussed the experience of “overworking” in the year leading up to their illness onset. In an anthropological study of the experience of CFS, Ware (1993) writes about individuals’ descriptions of working hard in the year or years leading up to their illness onset. Ware described this hardworking behavior in terms of “type A” and

“perfectionistic” characteristics that led many to feel exhausted. While some participants in the current study indicated stress or exhaustion in the year leading up to their illness, the majority described their hardworking styles in a positive manner. Furthermore, this hard work ethic was often described in order to show the stark contrast to their considerably more limited lives (functionally and socially) following illness onset. In fact, all 14 participants in the current study described having active lifestyles including a range of both work and recreational activities. The findings from the current study suggest that when assessing for factors related to stress and functioning leading up to the onset of ME and CFS, it would be beneficial to include questions that assess for whether these activities were deemed stressful or taxing, as this may have implications for illness attributions and whether stressful experiences and lifestyles are truly perceived as contributory to onset.

A majority (79%) of participants in the current study reported that they were relatively healthy prior to the onset of their illness. This finding is consistent with a qualitative study by Lovell (1999), which found that aid workers who developed CFS when living overseas considered themselves as healthy before the development of the illness. While the majority of participants in the current study considered themselves relatively healthy prior to onset, 79% also described notable health problems in the year or years leading up to the onset of the illness. Within this category, 36% described the experience of being frequently sick with colds or sore throats. A previous study conducted by this author and colleagues found that individuals retrospectively reported experiencing multiple health

symptoms prior to the onset of their fatiguing illness. These included Fukuda et al. (1994) symptoms, neurological impairments, sensitivities, cardiovascular symptoms, loss of thermostatic stability, pain, sleep disturbances, neurosensory, perceptual, and motor symptoms, neuroendocrine, and mood symptoms (Evans, Barry, Brown, & Jason, 2015). The presence of health problems and symptoms prior to the onset of the illness could potentially be identified as risk factors for ME and CFS. These health problems may also influence illness course and differentiate individuals with ME and CFS into subtypes (Evans et al., 2015).

Participants identified symptoms experienced during the onset of their illness. Specifically participants described symptoms that generally fell in the following categories: flu-like symptoms, digestive problems, pain, autonomic dysfunction, fatigue, post exertional malaise (PEM), sleep difficulties, and cognitive impairment. Two symptoms that were endorsed with the highest frequency were “exhaustion” (57%) and general cognitive difficulties (43%). In congruence with the tenets of qualitative description, the author made an effort to use words to describe symptoms that were also used by the participants themselves. It is notable that a large proportion of participants used the term “exhaustion” rather than only fatigue. Future surveys designed to assess early signs and symptoms within the onset period should consider using the participant’s preferred language for their symptoms. Overall, the identification of early signs and symptoms of the illness could be beneficial for early intervention and treatment.

Many participants described comorbid health conditions including fibromyalgia, POTS, and IBS. These findings are consistent with previous quantitative studies that have revealed that CFS is highly comorbid with fibromyalgia (Buchwald & Garrity, 1994), IBS (Whitehead, Palsson, & Jones, 2002), and POTS (Steward, Gewitz, Weldon, Arlievsky, & Munoz, 1999). Individuals with highly comorbid conditions may be at risk for developing ME and CFS, and they may also negatively influence the severity of onset and illness trajectory.

A majority (79%) of participants described the negative impact that exertion had on their symptoms and illness course. These exertional effects included both mental and physical exertion. Post exertional malaise (PEM) has been found to elicit a worsening of symptoms (e.g. fatigue, headaches, cognitive dysfunction etc.) following routine daily tasks including going to the grocery store, walking, and showering (Spotila, 2010). Jason et al. (1999) found up to 93.8% of individuals with CFS endorsed the experience of PEM depending on how the questions on a survey were worded. Furthermore, PEM has also been measured using objective methods (Light, White, Huguen, & Light, 2009).

Participants described both behavioral and mental/internal forms of coping in response to the onset of ME and CFS. Behavioral forms of coping included attempts to limit activities to prevent overexertion, attending support groups, and creating symptoms lists. In an earlier qualitative study on illness perceptions in individuals with CFS, Clements et al. (1997) also found that individuals described behavioral forms of coping such as pacing and reducing activities. Findings from

the current study as well as by Clements et al. (1997) also revealed that these strategies were considered most helpful to symptom management rather than as a cure for the illness. The pacing strategy endorsed by many individuals in the current study has been supported by the energy envelope therapy, which suggests that balancing perceived energy with expended energy can help individuals with ME and CFS conserve energy and reduce overexertion (Jason et al. 1999; Jason et al. 2010; Pesek, Jason, & Taylor, 2000). Other forms of coping described in the current study involved internal methods, such as a changing one's mindset. For example, many individuals described the development of a philosophical acceptance of the illness. This experience of gaining acceptance is consistent with Fennell's phase theory of CFS (1995) in which participants reach acceptance of the illness in phase three following the crisis and stabilization experiences in phase one and two. While the experience of acceptance was described by individuals following the initial crisis phase in the current study, some participants found acceptance relatively early on in their illness progression and even before reaching "stabilization."

Qualitative findings from the current study suggest that the onset of illness had an emotional impact on more than 50% of participants. Some participants described going through periods of depression, whereas others described fear, anger and a state of confusion regarding the onset of the illness. This is consistent with findings from a mixed method study by Tuck and Wallace (2000) who found that compared to a control group, women with CFS reported significantly higher levels of depression, anxiety, anger, and confusion following the onset of their

illness. The experience of depression following onset was corroborated in qualitative interviews (Tuck & Wallace, 2000). These findings suggest that the onset of ME and CFS can have a profound emotional impact on the sufferer. Individuals with ME and CFS could benefit from significant emotional and instrumental support from friends, family, and health providers during the earliest phase of illness development.

A large majority of participants described many ways in which the illness limited their lives in terms of work, social life and family responsibilities. Consistent with this finding, Schweitzer (1995) and Anderson and Ferrans (1997) found that individuals with CFS report significantly impaired quality of life. Furthermore, while a small subset of individuals described the support they received during the onset of ME and CFS (21%), half of participants described the lack of support they received from others (friends, family, and doctors) during the onset of the illness. A qualitative study by Dickson and Flowers (2007) found that CFS participants described a sense of loneliness, isolation, and lack of support from friends, family, and general practitioners. A needs assessment by Drachler et al. (2009) revealed that individuals with ME and CFS expressed the need for support in understanding and receiving a diagnosis, validation from health providers and family, as well as support in finding ways to engage in social activities. A mixed method study by Schoofs, Bambini, Ronning, Bielak, and Woehl (2004) found that individuals with CFS lack social support and their degree of perceived social support was correlated with quality of life factors. Jason, Witter, and Torres-Harding (2003) have provided evidence that perceived

social support is correlated with physical health outcomes in individuals with CFS. These previous findings in conjunction with the current findings suggest that individuals with ME and CFS are severely lacking a sense of support from others (health providers and family/friends) during the onset of illness and in the years following onset.

In addition to the limited perceived support, 43% also described limitations of the many treatments that they tried during the early development of their illness. Currently there is not a gold standard treatment for the illness due to the multidimensionality of the illness, the absence of a confirmed etiology, and the variability in case criteria for diagnosing the illness (Afari & Buchwald, 2014). A lack of social support and an absence of effective treatments available in the early stages of the illness likely has a negative impact on the course of illness and overall quality of life in individuals with this debilitating illness.

Overall, the qualitative findings provide insight into how individuals with ME and CFS describe and reconstruct their illness onset and progression. Findings of the current study revealed many commonalities with by Ray et al. (1998). Most notably, both studies reveal that ME and CFS onset is likely more complex than the dichotomous categorization of onset (sudden versus gradual) that is commonly described in the literature. Both studies found evidence for the experience of sudden, steadily progressing/gradual, and phased onset patterns. However, the current study findings differ from Ray et al. (1998), as participants in the current study were often included in more than one onset group. For example, an individual with a sudden onset could experience a steady progression

or a wax and wane illness pattern. These findings suggest that onset and illness progression may be even more complex and dynamic than Ray and colleagues (1998) have suggested. Furthermore, the current study findings suggest that onset and illness progression are closely tied together and constructs that are not easily differentiated (e.g. steady progression may describe an illness course as well as a gradual onset). Additionally, the current study found evidence of a “definitive turning point/downturn” in the ME and CFS illness progression, as well as a moment when participants realized that something was seriously wrong medically. These themes have significant clinical and research implications, as they denote a period in time in which an individual might pursue medical care and also begin the search for a diagnosis. A better understanding of the signs and symptoms that accompany these moments of insight might lead to interventions that focus on earlier points in the illness trajectory and for individuals who might have otherwise recognized the severity of their illness much later.

Timeline Graphs and Implications

Illness timeline graphs were created for all 14 participants from phase two of the current study. Eight participants provided feedback and corrections on their illness graphs and these are shown in Appendix C. The timeline graphs provide a visual display of functioning and disability over the ME and CFS illness trajectory (the period leading up to illness onset, at onset, and following onset). The graphs provide insight into periods of improvement and decline over the course of the ME and CFS illness, in the context of various life events, health experiences, and interventions/treatments.

The ME and CFS illness timeline graphs of the current study fit nicely within the trajectory framework of chronic illness by Corbin and Strauss (1991). Corbin and Strauss (1991) describe a trajectory as an illness course that is shaped by the ill individual, his/her family members, friends, and health care providers, over time. Different illness phases are described by Corbin and Strauss (1991) and they include the biographical and health events that are present before the onset of illness (pre-trajectory), the period of time in which symptoms and signs first appear (trajectory onset), life threatening emergencies (crisis phases), “active” illness periods that may require hospitalization (acute phases), periods in which the illness is relatively well managed (stable phases), periods of fluctuating illness that are poorly controlled (unstable phases), periods of illness progression/decline (downward phases), and lastly, the final phase of life (dying). These phases (with the exception of the dying phase) are made visible by the illness timeline graphs of the current study.

Corbin and Strauss (1991) discuss implications for thinking about chronic illness in terms of a trajectory. Specifically, an understanding of illness course can help one better manage disability and improve quality of life, help change or shape the course of illness, and more effectively manage symptoms. Furthermore, while health care providers may have an understanding of a patient’s medical course and treatment history, an illness trajectory can provide additional insight into the way in which individuals manage and shape their illness in the context of daily life (Corbin and Strauss, 1991). They point out that many of the strategies that are used to manage illness occur at home and not in medical offices or

hospitals. Furthermore, they discuss how a trajectory can reveal how pre-illness and pre-medical intervention experiences shape the way individuals understand and respond to their illness and to their health care providers (Strauss & Corbin, 1991).

Illness timeline graphs have many clinical and research implications within the ME and CFS context. Specifically, they allow for years of illness information to be displayed in a more digestible, visual format. Furthermore, the timeline graphs can be used by patients to track symptoms over time and to identify potential factors that contribute to periods of illness remission or decline. An individual with ME and CFS may identify a period in his/her illness course when a certain medication or behavioral coping strategy (e.g. pacing) was associated with an improvement in functioning and quality of life. Henly, Wyman, and Findorff (2011) have also described how the process of tracking illness trajectories can highlight factors that contribute to illness changes and can allow patients to potentially take control over their illness course. In the current study, one participant, who described herself as a “highly visual person,” reported that the opportunity to see the peaks and valleys of her functioning over time provided her with heightened clarity about her illness experience.

The process of visually tracking ME and CFS illness progression may help to identify different subtypes of the illness, which then may help health care providers tailor treatments to the individual. A person who has had a slow and downward progression of their ME or CFS would likely benefit from different treatments/recommendations than an individual who has demonstrated a wax and

wane and unpredictable illness course. Additional research on pre-trajectory, trajectory onset, and illness course patterns may also lead to the identification of early signs/symptoms and methods that focus on early intervention/prevention of the illness.

Visual illness timelines have been used previously in health research. A study by Lunney, Lynn, Foley, Lipson and Guralnik (2003) utilized graphical timelines to show that end of life functioning was highly variable across four different types of end of life trajectories (e.g. sudden death, cancer death, death from organ failure, and frailty). The authors suggested that the health trajectories can be used to tailor end of life interventions to the individual in order to improve overall quality of life. Another study by Bausewein and colleagues (2010) used graphical timelines to show the trajectory of breathlessness in individuals with chronic obstructive pulmonary disease (COPD). Their findings showed that those who have worsening or fluctuating breathlessness trajectories may have a more difficult time predicting and controlling the symptom and likely require individualized treatment. Similar methods could be used for understanding illness patterns in individuals with ME and CFS.

Further still, illness graphs can be used as communication tools for patients who are meeting with new health care providers and who might not have a full understanding of a patient's illness history and course. Patients can use the graphs to provide their health care providers with a sense of how their symptoms have changed over time, the various treatments that they have tried, and whether the illness is worsening. Cognitive difficulties including word finding and brain

fog difficulties are cardinal symptoms of ME and CFS. Many participants in the current study discussed how these problems make it extremely difficult to have a conversation. Therefore, a visual graph of their illness trajectory may be easier to share with a health provider than providing a verbal account of their illness history. Additionally, The sharing and co-construction of an illness history between patient and health care provider may increase the degree of support and validation that patients receive at their medical visits. Kleinman (1988) refers to a patient care model called “empathic witnessing” in which there is an “existential commitment to be with the sick person and to facilitate his or her building of an illness narrative that will make sense of and give value to the experience” (p. 54). This act of witnessing and sharing an illness narrative has been described as a co-construction between patient and physician (Verghese, 2001) and is theorized as a way to promote validation and empathic interactions between patients and health care providers. Corbin and Strauss (1991) discuss how pain patients who present to a health clinic are often coming with years of health experiences that influence how they react to treatment and to their providers. Specifically, they discuss how a patient who is branded as “difficult” by a health care provider is likely reacting to past experiences and interactions with previous providers (Fagerhaugh and Strauss 1977 as cited in Corbin & Strauss, 1991). Knowledge of a person’s illness history and previous interactions within the healthcare system can help providers shape the attributions they make about patients and it can lead to increased empathy and support. Given the lack of support that many participants in the current study experienced from health providers, friends, and family members, the

illness timelines may provide a way for health care providers to better connect with their patients on an empathic level.

Limitations

The samples in phase one and phase two of the current study were not selected through random assignment; thus, participants in the current convenience sample may have different qualities than a more representative population of individuals affected by ME and CFS. For instance, in both phase one and two, participants were largely White women and middle aged. Based on research by Jason and colleagues (1999), CFS occurs at higher rates in African-American and Latino samples. Another limitation of the current study is the retrospective nature of the self-report method and qualitative interviews. Participants provided self-reported information on their illness onset, which in many cases occurred many years prior. It is possible that their responses are biased due to recall difficulties that occur when remembering remote events. While the potential for recall bias is a limitation of the current study, highly salient information is often recalled more accurately than less salient information (Cannell, Marquis, & Laurent, 1977; Dawson, Kanim, & Sra, 2002; Stull et al., 2009). The majority of individuals in the current study described their onset period as a “life changing” and a salient period in their life.

There is significant variability in the ME and CFS literature with regard to the way in which sudden versus gradual onset is defined. Furthermore, differences across samples (e.g., community based versus tertiary) and across case definitions used to select for ME and CFS increases the difficulty in comparing the results of

the current study with previous findings. The current study defined sudden onset as occurring between 24 hours to one month, and gradual as any onset greater than one month. This decision was based on previous research, in which sudden onset was defined as up to one month (Jason et al., 2000). Unfortunately there is not yet a uniform definition for mode of illness onset, thus contributing to the wide variety of onset definitions in the literature. For example, Salit (1997) defined sudden as occurring in conjunction with an “acute precipitating event,” whereas gradual onset was defined as any onset that did not have an “acute precipitating event” (p. 61). Similarly DeLuca et al. (1997) described sudden onset as viral with a clear onset date and gradual onset was defined as slowly progressing over “weeks to several months or greater” (p. 85). Overall, differences in methodology, onset categorization, diagnostic criteria, and sample selection across studies make the comparability of onset differentiation on key factors of ME and CFS a complicated endeavor.

Conclusions and Future Directions

Overall, results of the current study did not provide evidence that mode of illness onset (defined as sudden versus gradual) differentiated patients on factors related to etiology, psychopathology, and prognosis. However, qualitative findings and illness timeline graphs revealed that ME and CFS onset experiences are likely more complex than the dichotomous sudden versus gradual categorization that is ubiquitous in the ME and CFS literature. The findings of the current study are aligned with recommendations for future research that were suggested by Ray et al. (1998). Ray et al. (1998) recommended that future studies

should involve the investigation of different etiological onset patterns as well as the potential interactions between various causal factors (e.g. infection, stress, and overexertion) and the degree of risk that these pose for the future development of the illness. In addition to these recommendations, the current study findings suggest that onset and illness progression may be even more dynamic and complex than is described by Ray et al. (1998). Specifically, the onset patterns revealed in the current study do not appear to be mutually exclusive (e.g. patients may identify with both sudden and steadily progressing/gradual onsets). These findings point to the need for further assessment of illness onset patterns and progression on larger and more representative populations. Furthermore, it is recommended that surveys designed to assess the onset experience include more than one question to assess mode of illness onset and illness patterns. In order to capture the complex ME and CFS onset experiences, surveys might include questions that assess the period of time in which an individual's first symptoms were experienced, whether the individual perceived their onset as sudden (regardless of the period of time that their first symptoms developed), whether the illness progression was initially noticed, and whether it progressed in the form of a steady progression or a cyclical "wax and wane" pattern. Furthermore, it would be beneficial to ask individuals about how long it took in days, months, and/or years until they experienced a "definitive turning point" in which functioning significantly decreased, as well as when they experienced a period of reflection in which the illness was perceived as something more serious than a typical sickness such as the flu (See Appendix D for a sample onset questionnaire).

A recent study found that participants who met criteria for ME with an acute onset had greater physical function impairment as well as physical, mental, and cognitive problems than individuals who met CFS criteria. These findings suggest that the combination of mode of illness onset and case criteria may be important for identifying subtypes of the illness. More research on the interaction between case criteria and onset patterns and the potential impact these have on health outcomes is also recommended.

Given the potential for recall bias when conducting a retrospective investigation of ME and CFS onset patterns, future studies might employ prospective methods in order to track individuals' onset patterns as they develop. There has been an influx of ecological momentary assessment techniques in health research for the purpose of tracking health symptoms and conditions over time (e.g., Steptoe, Gibson, Hamer, & Wardle, 2007 and Stone & Shiffman, 1994). These real time methods for tracking health could also be used to construct visual graphs that map symptoms and functioning over time, which could lead to interventions aimed at prevention. Furthermore, the current study revealed that many participants realized too late that exertion worsened their illness. If illness timeline graphs were developed in real-time, early intervention may be possible, which may also lead to better health outcomes. Future studies might also investigate ways to develop efficient methods that allow patient's to develop illness timelines graphs themselves. This would allow patients to visualize and monitor their illness trajectory as well as communicate their illness experience to health care providers. Lastly, future research studies that have a

focus on onset assessment should utilize survey questions that more effectively assesses onset experiences. Specifically, an onset survey should include questions regarding the period of time in which first symptoms are developed, whether participants perceive their onset as sudden, steadily progressing, waxing and waning, or improving, and at what point in the patient's illness course they realize the need to seek specialized medical treatment. Additionally, the survey should assess for early signs and symptoms, as these may be important risk factors for the development of the illness. A survey specifically designed to assess onset patterns in a large and representative sample of individuals with ME and CFS could provide valuable information about the prevalence of different onset patterns and the potential for these patterns to differentiate patients on key factors including etiology, illness course, and prognosis.

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Appendix A

The DePaul Onset Interview Protocol

DePaul Onset Interview

Opening Script:

Thank you for participating in our study. During this phone interview I will be asking you questions about your health and illness experiences.

This phone interview will take approximately 1 hour to complete. You also have the option of breaking up this interview into two 30-minute interviews if that is preferable. There may also be an additional follow up phone interview on a different day that will take approximately 30 minutes to complete.

Please remember that you do not have to answer any questions that you do not feel comfortable answering and do let me know if you need to take a break or have any questions or concerns during the interview. Please answer the questions to the best of your ability.

Preliminary Question:

Before we begin, please tell me which illness label you use to describe your illness. For example, do you prefer to refer to your illness as chronic fatigue syndrome/CFS, myalgic encephalomyelitis/ME, or ME/CFS? Or do you use a different label?

Main Questions

1. Please tell me about the period of time when you first became sick with ME/CFS (*use preferred illness label*)

**Additional follow questions to be asked as needed (i.e. if participants do not provide this information following the initial prompt):*

Please tell me about the early days, weeks, and months of your illness

Please describe to me how your illness developed during this time

Please tell me more about this experience

What else do you remember about that experience?

What else do you remember about that period of time?

Please describe how you were feeling physically

Please describe how you were feeling emotionally

2. Please tell me about the period of time before you became sick with ME/CFS

**Additional follow up questions to be asked as needed (i.e. if participants do not provide this information following the initial prompt):*

Please tell me about the year before you became sick with ME/CFS

If you can, please tell me about your life just before you became sick with ME/CFS

Please tell me more about that experience

What else do you remember about that experience?

What else do you remember about that period of time?

Please describe how you were feeling physically

Please describe how you were feeling emotionally

If not already answered ask:

3. “Over what period of time did your first symptoms develop?”

Timeline questions

Comments for interviewer: The purpose of this portion of the interview is to determine **how participants’ functioning levels changed over the course of their onset, directly prior to their onset and after their onset.** Participants will be asked to refer to the **Bell CFS Disability Scale** and rate their disability using this scale from 0-100.

Participants will be asked to **rate their disability level before, during, and after illness onset and/or first symptoms.** Additionally, the interviewer **should ask questions about significant events and symptoms occurring at time of initial onset, and during peaks in disability level and decreases in disability level** (e.g. for example, if a participant experiences an additional 20 point decrease in disability following illness onset/initial CFS symptoms, the interviewer should

ask what was occurring during this timeframe and what symptoms were experienced).

***If not already provided, ask participants to identify what year, month, time of year/season (if remembered), they first developed ME/CFS**

***Ask participant to identify whether personal experiences/events or holidays were coinciding with their illness development** (*These memorable events can help participants recall their onset experience*).

Year _____

Month _____

Season _____

Personal Events/Holidays _____

Functioning Questions

4. Please review the CFS Disability Scale and please tell me to the best of your ability what you would rate your disability level when you first became sick with symptoms of ME/CFS

Please note: *It is important to be flexible and follow each participant's story and ask about functioning level as they describe their illness history.*

Additional areas to cover:

Make sure to also ask about functioning level (using 0-100 scale) for the following areas:

Just prior to illness onset/Year before illness onset:

Directly following onset (i.e. how did functioning change after first symptoms/onset?):

How did functioning change in months or years following onset?

Symptoms and Significant Events

Please note: *It is important to be flexible and follow each participant's story and ask about symptoms and significant events as they describe their illness history.*

If not already provided: What were the first symptoms that you experienced?
When did you experience these symptoms?

Also get information regarding:

Symptoms during **peaks** in functioning

Symptoms during **decreases** in functioning

Make sure to gather information about:

Significant events (personal, work, or health related) that occurred at
illness onset and/or during **time of first symptoms**

Significant events during **peaks** in functioning

Significant events during **decreases** in functioning

Appendix B

Bell's CFS Disability Scale

Bell- CFS Ability Scale

100: No symptoms with exercise. Normal overall activity. Able to work or do house/home work full time with no difficulty.

90: No symptoms at rest. Mild symptoms with physical activity. Normal overall activity level. Able to work full time without difficulty.

80: Mild symptoms at rest. Symptoms worsened by exertion. Minimal activity restriction needed for activities requiring exertion only. Able to work full time with difficulty in jobs requiring exertion.

70: Mild symptoms at rest. Some daily activity limitation clearly noted. Overall functioning close to 90% of expected except for activities requiring exertion. Able to work/do housework full time with difficulty. Needs to rest in day.

60: Mild to moderate symptoms at rest. Daily activity limitation clearly noted. Overall functioning 70% to 90%. Unable to work full time in jobs requiring physical labor (including just standing), but able to work full time in light activity (sitting) if hours are flexible.

50: Moderate symptoms at rest. Moderate to severe symptoms with exercise or activity; overall activity level reduced to 70% of expected. Unable to perform strenuous duties, but able to perform light duty or deskwork 4 - 5 hours a day, but requires rest periods. Has to rest/sleep 1-2 hours daily.

40: Moderate symptoms at rest. Moderate to severe symptoms with exercise or activity. Overall activity level reduced to 50-70% of expected. Able to go out once or twice a week. Unable to perform strenuous duties. Able to work sitting down at home 3-4 hours a day, but requires rest periods.

30: Moderate to severe symptoms at rest. Severe symptoms with any exercise. Overall activity level reduced to 50% of expected. Usually confined to house. Unable to perform any strenuous tasks. Able to perform deskwork 2-3 hours a day, but requires rest periods.

20: Moderate to severe symptoms at rest. Unable to perform strenuous activity. Overall activity 30-50% of expected. Unable to leave house except rarely. Confined to bed most of day. Unable to concentrate for more than 1 hour a day.

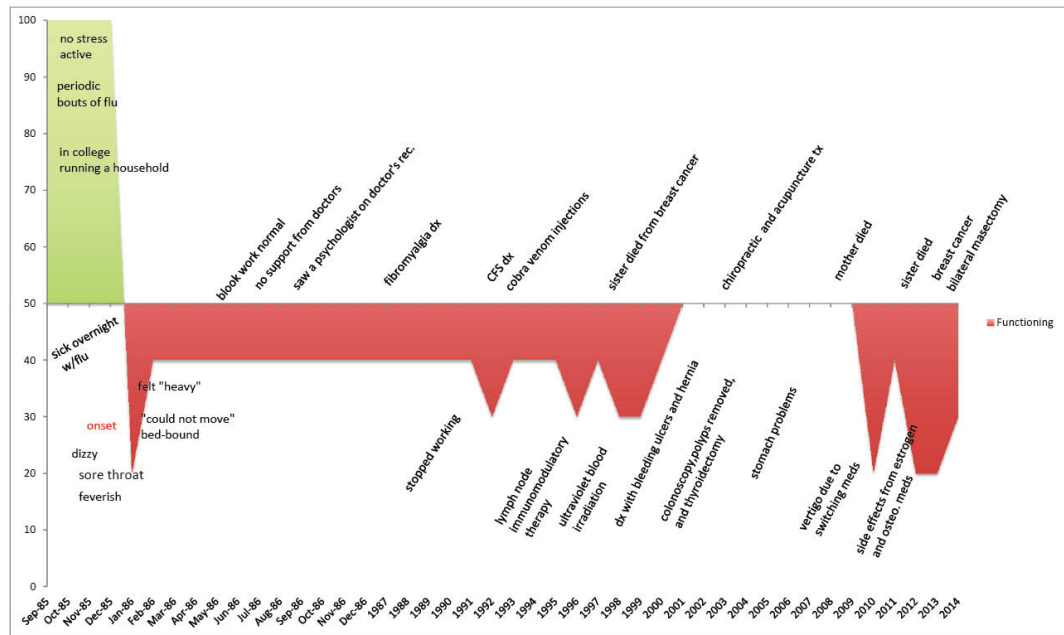
10: Severe symptoms at rest. Bed ridden the majority of the time. No travel outside of the house. Marked cognitive symptoms preventing concentration.

0: Severe symptoms on a continuous basis. Bed ridden constantly, unable to care for self.

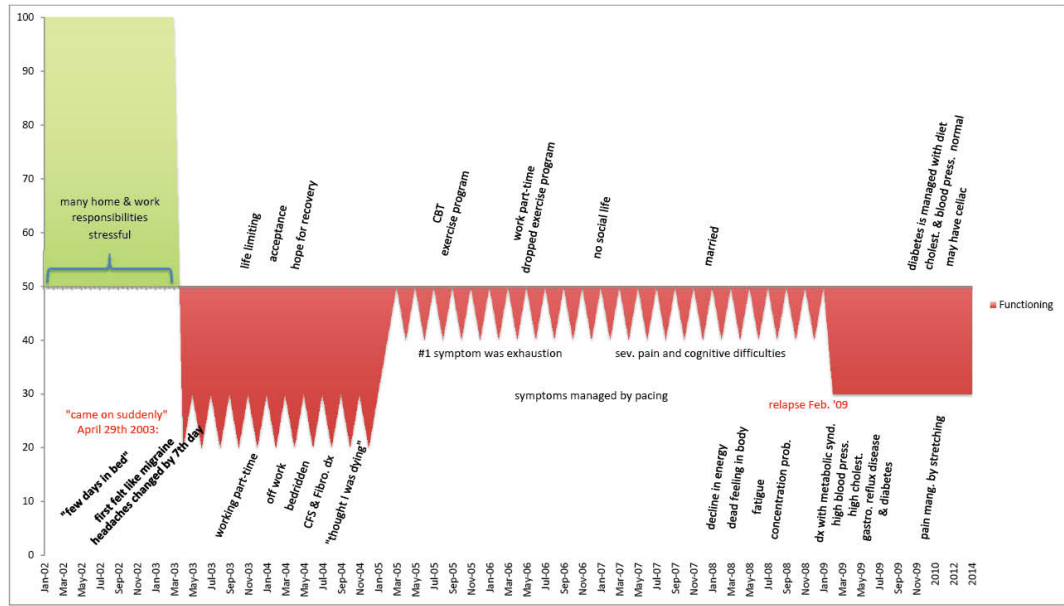
Appendix C

Participant Reviewed/Corrected Illness Timeline Graphs

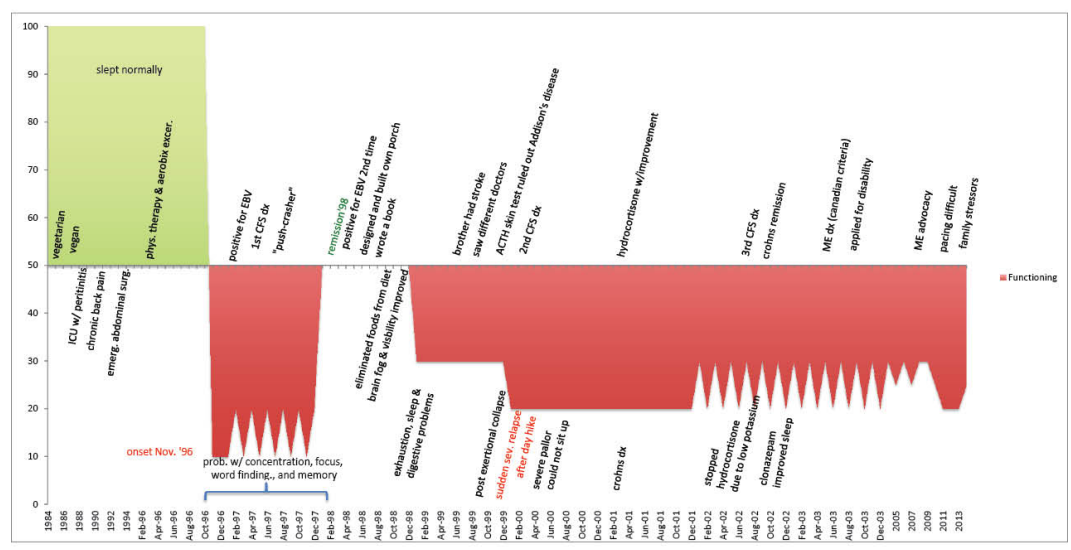
Participant 9 – 24 Hour Onset



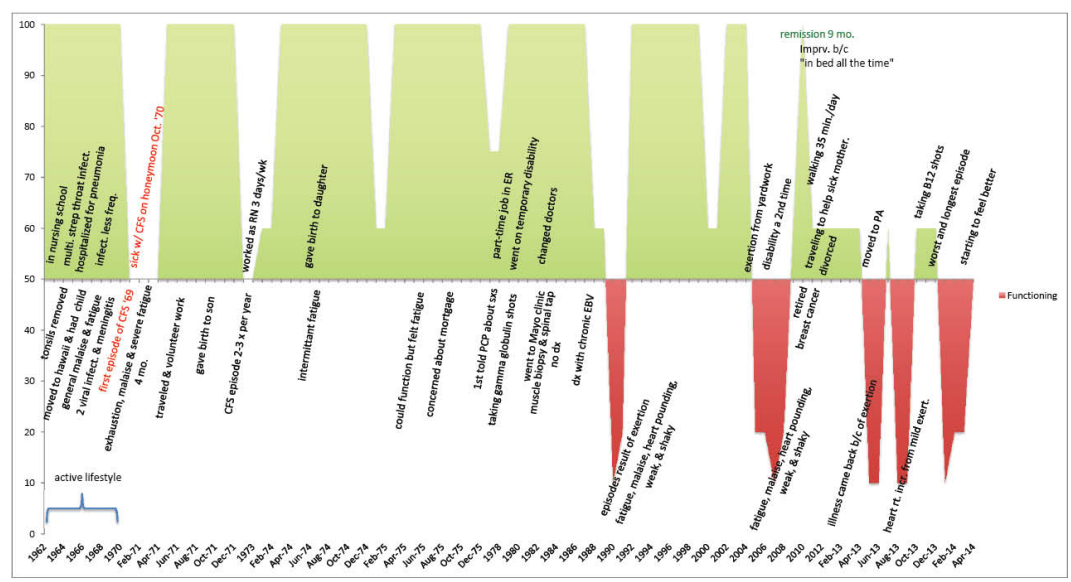
Participant 3 – Onset Over 24 Hours



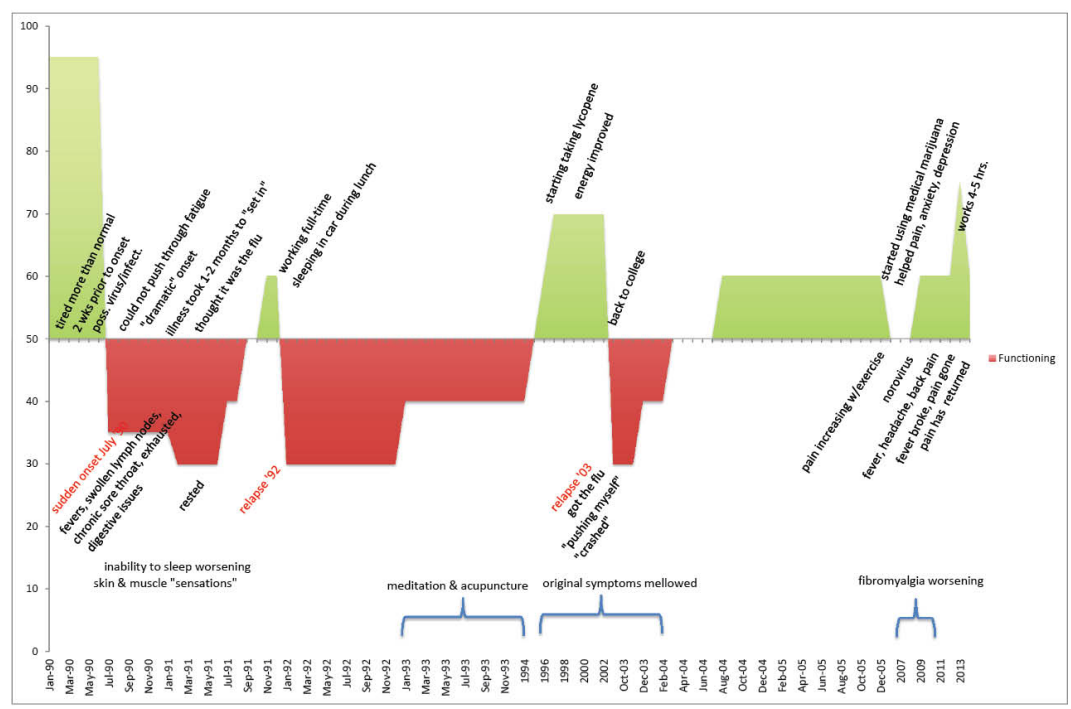
Participant 5 – Onset Over 1 Month



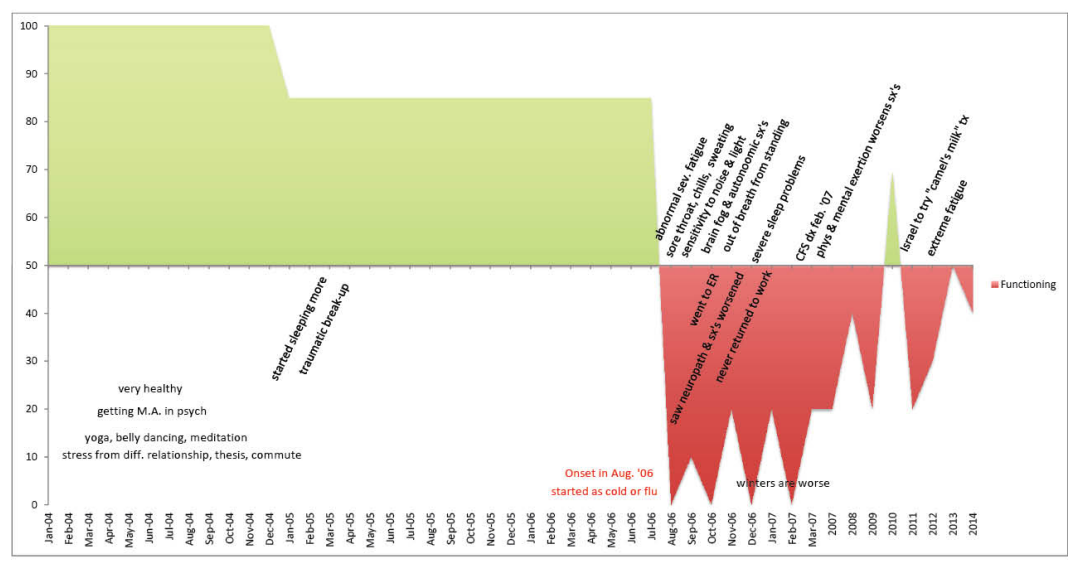
Participant 7 – Onset Over 2 to 6 Months



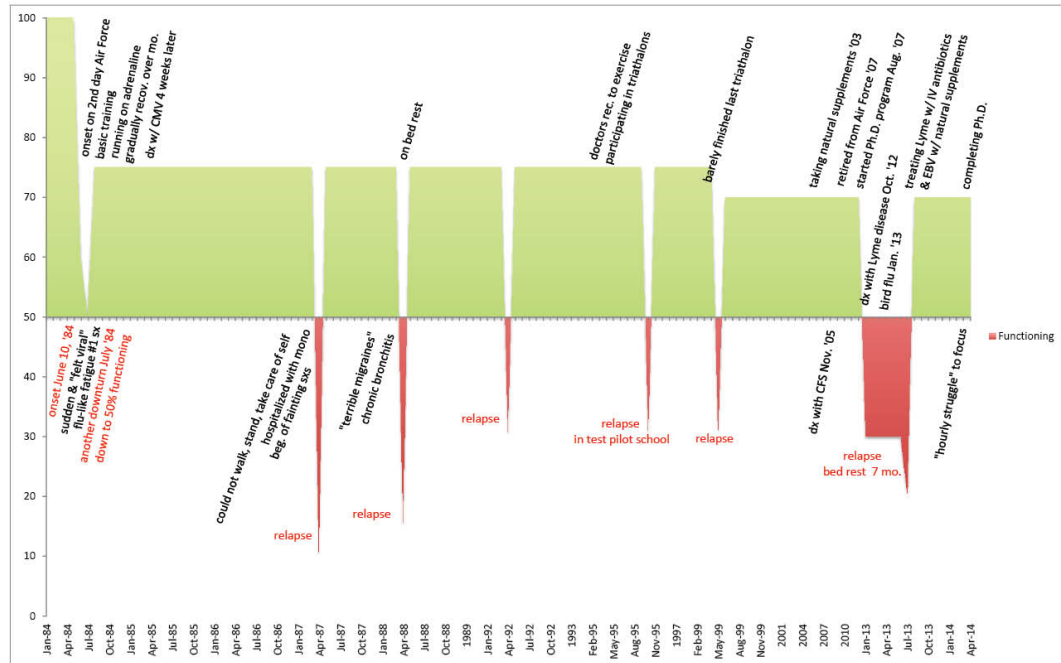
Participant 10 – Onset Over 2 to 6 Months



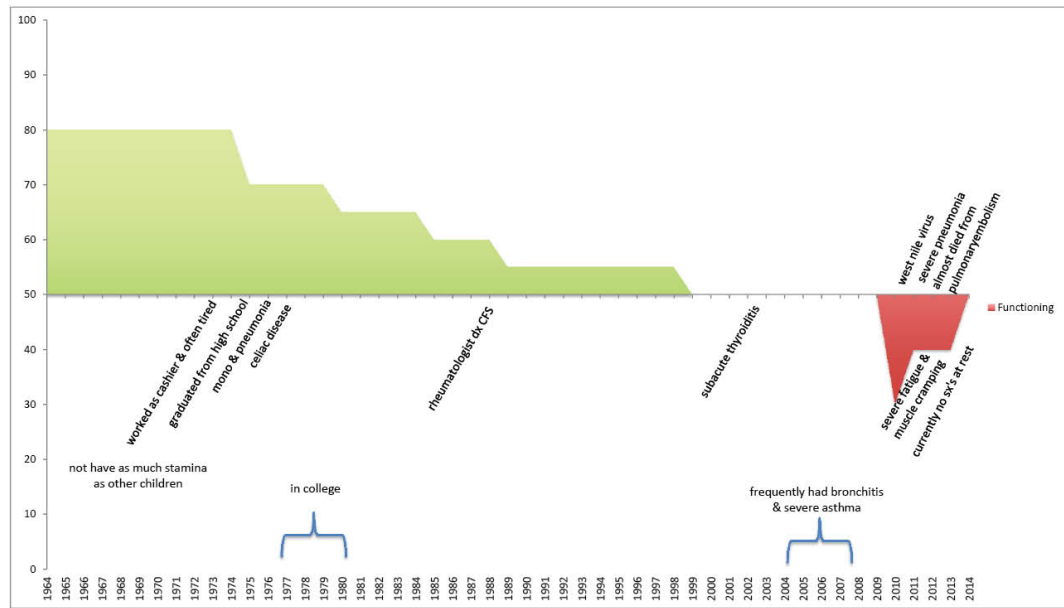
Participant 1 – Onset Over 7 to 12 Months



Participant 11 – Onset Over 3 or More Years



Participant 8 – Onset Over 3 or More Years



Appendix D

Sample ME and CFS Onset Questionnaire

ME and CFS Onset/Illness Progression Questionnaire

1. Please circle the response below that best describes the period of time in which your first symptoms of ME or CFS developed?
 - a. Over 24 hours
 - b. Over 1 week
 - c. Over 1 month
 - d. Over 2 to 6 months
 - e. Over 7 to 12 months
 - f. Over 1 to 2 years
 - g. Over 3 or more years
2. Over what period of time did your ME or CFS illness develop? _____
3. Did you notice your illness progression initially?
 - a. Yes
 - b. No
4. Did you experience a sudden onset of your ME or CFS illness?
 - a. Yes
 - b. No
 - c. I do not know
5. How would you describe your ME or CFS onset?

6. Please circle the response below that best describes how your ME or CFS illness has progressed over time.

- a. Steady progression (symptoms and disability accumulate in severity/intensity over time)
 - b. Wax and Wane (symptoms and disability have a fluctuating pattern that includes multiple periods of improvement and decline over time).
 - c. Other. Please describe: _____
7. At what point during your illness progression did you experience your most severe decline in functioning/symptoms?
- a. At onset
 - b. Within one week of onset
 - c. Within one month of onset
 - d. Within 2-6 months of onset
 - e. Within 7-12 months of onset
 - f. Within 1-2 years following onset
 - g. Within 3 or more years following onset
 - h. I do not know
 - i. Other. Please describe: _____
8. When during your illness progression did you realize that your illness was more than a typical sickness such as the flu?
- a. At onset
 - b. Within one week of onset
 - c. Within one month of onset

- d. Within 2-6 months of onset
 - e. Within 7-12 months of onset
 - f. Within 1-2 years following onset
 - g. Within 3 or more years following onset
 - h. I do not know
 - i. Other. Please describe: _____
9. At what point in your ME or CFS illness progression did you realize that you needed specialized medical care?
- a. At onset
 - b. Within one week of onset
 - c. Within one month of onset
 - d. Within 2-6 months of onset
 - e. Within 7-12 months of onset
 - f. Within 1-2 years following onset
 - g. Within 3 or more years following onset
 - h. I do not know
 - i. Other. Please describe: _____