The Voice of the Patient

A series of reports from the U.S. Food and Drug Administration’s (FDA’s) Patient-Focused Drug Development Initiative

Chronic Fatigue Syndrome and Myalgic Encephalomyelitis

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Introduction

On April 25, 2013, FDA held a public meeting to hear perspectives from patients with chronic fatigue syndrome (CFS) and myalgic encephalomyelitis (ME) about their disease, its impact on their daily life, and currently available therapies. For this meeting and summary report, the terms CFS, ME, and CFS and ME are used interchangeably in describing the conditions.\(^1\) CFS and ME is a serious disease or set of diseases for which there are currently no FDA-approved therapies.

FDA conducted the meeting as part of the agency’s Patient-Focused Drug Development initiative, an FDA commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) to more systematically gather patients’ perspectives on their condition and available therapies to treat their condition. As part of this commitment, FDA is holding at least 20 public meetings over the next five years, each focused on a specific disease area. More information on this initiative can be found at [http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm](http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm).

The April 25 Patient-Focused Drug Development meeting was part of a larger two-day workshop to explore important issues with respect to the development of safe and effective drug therapies for CFS and ME. The second day (April 26) focused on a technical discussion on issues such as clinical trial design, outcome measures, regulatory issues, and possible pathways to expedite treatments. This report summarizes the input provided by patients and patient representatives at the April 25 meeting. The archived webcast and transcript for the April 25 meeting are available on the meeting webpage. A separate summary report of the April 26 proceedings is planned.

Report overview

The April 25 Patient-Focused Drug Development meeting gave FDA the opportunity to hear directly from patients, patient caretakers, and other patient representatives about their experiences with this debilitating condition. The discussion focused on two key topics: (1) disease symptoms and daily impacts that matter most to patients and (2) patients’ perspectives on current approaches to treating CFS and ME. The questions for discussion (Appendix 1) were published in a Federal Register notice that announced the meeting.

For each topic, a panel of patients and patient representatives (Appendix 2) shared comments to begin the dialogue. Following panel comments, a facilitated discussion invited comments from other patients and patient representatives in the audience. An FDA facilitator led the discussion, and a panel of FDA staff (Appendix 2) asked follow-up questions. Participants who joined the meeting via live webcast were able to submit comments. To supplement the input gathered at the meeting, patients and others were encouraged to submit comments on the topic to a public docket,\(^2\) which was open until August 2, 2013. More information on the meeting, including the archived webcast and transcript, is available on the meeting webpage (http://www.fda.gov/Drugs/NewsEvents/ucm319188.htm).

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\(^1\) The terms CFS and ME are intended to be inclusive and make no judgment on the cause of different symptom complexes. At this time, FDA does not endorse any particular disease definition. Drug development focuses on quantitative measures of benefit (e.g., symptom improvement) in a patient population. FDA expects drug developers to define the disease using detailed enrollment criteria for clinical trials that exclude other known causes of fatigue and similar symptom complexes.

\(^2\) A docket is a repository through which the public can submit electronic and written comments on specific topics to U.S. federal agencies such as FDA. More information can be found at [www.regulations.gov](http://www.regulations.gov).
In addition to this summary of the input provided by patients and patient representatives at the April 25 meeting, this report contains a summary of comments submitted to the docket, beginning on page 13. The report is intended to reflect the content of this meeting and the docket comment submissions as they relate to patient perspectives on disease symptoms, impacts, and current treatments. The report is not meant to be representative in any way of the views and experiences of any specific group of individuals or entities. There may be symptoms, impacts, treatments, or other aspects of the disease that are not included in the report.

The patient input generated through the April 25 Patient-Focused Drug Development meeting and docket comments strengthens our understanding of the burden of CFS and ME on patients and the range of treatments currently used to treat CFS and ME and its symptoms. FDA staff will carefully consider this input as it fulfills its role in the drug development process, including when advising sponsors on their drug development programs and when assessing products under review for marketing approval. For example, Appendix 3 shows how this input may directly support our benefit-risk assessments for products under review. This input may also be of value to the drug development process more broadly. For example, the report may be useful to drug developers as they explore potential areas of unmet need for CFS and ME patients. It could also point to the potential need for development and qualification of new outcome measures (e.g., relating to cognitive functioning) in clinical trials.

Overview of CFS and ME

CFS and ME is a complex, debilitating disease characterized by profound fatigue lasting for six or more consecutive months that is not improved by bed rest and that may be worsened by physical or mental activity. The exact cause or causes of CFS and ME are unknown. Symptoms affect several body systems and may include post-exertional malaise, unrefreshing sleep, weakness, muscle and joint pain, impaired memory or mental concentration, tender lymph nodes, sore throat, headaches, and insomnia. The nature and severity of symptoms vary from person to person, and diagnosis is challenging because there are no specific tests for the disorder.

According to the Centers for Disease Control and Prevention, between 1 and 4 million people in the United States are afflicted with CFS. Although most common in 40- to 60-year-old women, CFS and ME affects both genders and all racial, age, and socioeconomic groups. The disease may occur with a sudden onset, such as following an infection, or it may occur with a gradual onset. Some patients improve spontaneously; however, many patients experience a prolonged course of illness with either periods of remission and exacerbation or steady decline. Currently, there are no approved therapies indicated to treat CFS and ME, and various off-label prescription, non-prescription, or non-drug therapies are used to manage symptoms or to target potential underlying causes of symptoms.

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3 The public was also able to provide input at the April 25 meeting on other issues related to drug development, through an open public comment session. These comments are available through the meeting transcript and archived webcast, but are not summarized in this report.

4 Refer to the Centers for Disease Control and Prevention website at http://www.cdc.gov/cfs/news/features/.
Key themes

The input FDA received through the meeting and the public docket underscore the chronic and serious nature of CFS and ME. Several key themes emerged from the meeting and submitted docket comments:

- Many patients can pinpoint a specific time in their life when they contracted the disease. Prior to contracting CFS and ME, many patients were highly productive and successful professionals or students. They now struggle with even the simplest aspects of day-to-day living.
- Patients struggle daily with their symptoms. Of over 50 symptoms identified, the most frequently mentioned included severe fatigue or exhaustion, impairments in cognitive functioning (e.g., concentrating or processing information), chronic pain, sleep difficulties, blood pressure drops and dizziness, sensitivity to light, sound and temperature and susceptibility to infection. The type, nature and severity of symptoms can vary from patient to patient.
- Post-exertional malaise or PEM (which participants believe is more aptly termed a “crash” or “collapse”) is a severe exacerbation of those cognitive and physical symptoms. A crash can result from even minimal mental or physical exertion, can happen without warning, and can last for days, weeks, months, or even years.
- Patients use or have tried a complex regimen of drug and non-drug therapies to treat their disease and manage their symptoms. Appendix 4 lists the therapies mentioned during this meeting or in comments submitted to the docket. These treatments have been met with varying degrees of effectiveness, and for some, none is effective. These treatments are often associated with bothersome side effects, which can, for example, exacerbate other symptoms of their disease (e.g., by causing drowsiness).
- CFS and ME takes a devastating toll on the lives of many patients and their families, including loss of careers, decreased quality of family life, social isolation, and feelings of hopelessness.
- Patients are desperate for research and development of treatments that can: (a) better relieve their most significant symptoms and (b) address the underlying cause(s) of their disease.

Discussion Topic 1: Disease Symptoms and Daily Impacts That Matter Most to Patients

The first topic focused on patients’ experiences with symptoms and the resulting impacts they exert on patients’ daily life. FDA was particularly interested in hearing about specific activities that are important to patients that they can no longer do at all or as fully as they would like because of their condition.

Five panelists provided comments to start the dialogue. Three CFS and ME patients participated, including: a physician living with the disease for more than 25 years who is “still able to work but struggles to make it through each day”; a former military linguist living with the disease for eight years, who is in his “seventh year of a two-year Master’s program”; and a former lawyer living with the disease for 23 years who is now largely housebound. Another panelist was a caretaker of two young adult children who have each lived with the disease for eight years and who are “nearly housebound,” having had to give up their academics and competitive athletics. Finally, the panel included a representative
from a patient advocacy organization that conducted a survey of CFS and ME patients.5

The panel’s testimonies painted a powerful picture of what it is like to live with this disease. Their statements primarily focused on: (a) the significant impairments in cognitive functioning and (b) the debilitating crashes or collapses (PEM) that can be triggered with even minimal physical or cognitive exertion, exacerbate all their other symptoms, and require days, weeks, or months to recover. They also described their daily struggle with pain, exhaustion, flu-like symptoms, orthostatic intolerance, and sensitivity to light and sound, among other chronic symptoms.

In the large-group facilitated discussion that followed the panel discussion, nearly all patients and patient representatives in the audience indicated by a show of hands that their experiences (or those of loved ones) were reflected in the panelists’ comments. Some participants said that they could still function in society while others reported that they were virtually housebound. Many could pinpoint the specific time in their lives when their symptoms began, after battling a flu or other illness, or just “waking up one morning” and not feeling well.

Participants stressed that the impact of CFS and ME is much larger than simply feeling fatigued. The range of cognitive and physical symptoms discussed by participants are described in more detail below, followed by a summary of the discussion on PEM, or crashes.

Cognitive symptoms

The most frequently described symptoms were a range of chronic impairments to cognitive functioning. By a show of hands, many participants appeared to share the perspective expressed by a participant that “[the] most debilitating symptoms fall under the rubric of neurological and cognitive dysfunction.”

Participants described their overall general cognitive dysfunction using terms such as “brain fog,” “impaired executive function,” and “neurocognitive problems.” They described specific manifestations of their cognitive dysfunction including “confusion,” “disorientation,” “hard to concentrate, can’t focus,” “inability to process information,” “can’t find the right words,” “inability to multi-task,” “slowed processing speed,” “impaired working memory,” “stuttering,” “slow reaction times,” “short-term memory loss,” “expressive dysphagia,” “dyslexia,” “inverting words and numbers when speaking or reading,” and “problems with decision-making.” A webcast participant described “‘mapping dyslexia,’ where I lose all sense of how to get from place to place, even with familiar locations.”

Participants described the impact that these cognitive symptoms have on their daily lives:

- Some reported an inability to conduct basic activities that they previously had no problems with prior to their illness, particularly reading, writing, or speaking in front of people. As a participant who is working on his master’s thesis said, “I read [what I’ve written] the next day and it’s not

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5 The Chronic Fatigue and Immune Dysfunction Syndrome (CFIDS) Association of America conducted a web survey aligned with the questions posed by FDA in the Federal Register notice (see www.cfids.org for more information). Another survey was conducted by a Lily Chu, a physician living with CFS, and Leonard Jason, a CFS researcher (contact lilyxchu@gmail.com for more information). Preliminary findings of both surveys were described at the April 25 meeting and the final results of both surveys were submitted to the public docket and are described in the section of the report entitled Summary of Comments Submitted to the Public Docket.
making sense to me. Now, does that mean I was confused when I wrote it and the writing is actually no good, or am I confused now and unable to read a perfectly good sentence?”

- Some described how cognitive impairment leads to the ability to concentrate for only very short periods of time (e.g., not longer than 15-20 minutes) and only a few times per week.

- Some described difficulty communicating or interacting with people, finding decision-making “very stressful,” and difficulty participating in social situations.

**Physical symptoms**

Beyond the impact on their cognitive functioning, participants described in detail a number of physical symptoms or other manifestations of their disease:

- Participants described in detail their experience with **severe fatigue, exhaustion, weakness, and lack of energy**. Many participants reported an inability to stand for even a few minutes, walk even a few blocks without exhaustion, or to sustain an activity for any significant length of time. In addition, patients described feeling drained, as well as having difficulty recovering strength and energy following physical exertion.

- Many participants indicated that they suffer from “**unrefreshing sleep,**” **insomnia and sleep disturbances.** As one participant explained, “I could sleep 10 to 12 hours a night, and I do, and I still don’t feel good in the morning… if I get less than 10 to 12 [hours] or if I have a bad night for whatever reason, I feel even worse.” One caretaker commented that sleep studies have shown that her daughter “gets zero slow-wave sleep, even with sleep medications.”

- Many participants described experiencing some form of **chronic pain,** including muscle and joint pain, headaches or migraines, pain behind the eyes, neck pain, neuropathic or nerve pain, and stomach pain. Participants discussed the wide variability in patients’ experiences with pain and expressed concern about the lack of knowledge about the fundamental causes of the pain suffered by people with CFS and ME. A few attributed their pain to a lack of oxygen in their body. A few commented that they also have fibromyalgia, but, as one participant explained, “I have pain issues but it’s not [all because of my] fibromyalgia.”

- Many participants indicated, by a show of hands, that they get a recurrent **sore throat** upon exceeding their physical or cognitive limits. As one panelist described: “Within 24 hours [of exertion], I’ll have a sore throat…it doesn’t follow the normal course of a 7- to 10-day viral illness, but it’s more of an inflammatory response.”

- Some reported **sensitivity to light, sound, and other stimuli,** and for a few it is extreme to the point of being unable to leave their home. As one participant described, “I cannot focus if faced with too much visual or sound stimulation, for example, too many objects in a store, music in a restaurant, or busy websites. I get dizzy, spatially disoriented, lose my balance, come down with headaches, and feel nauseated in such environments.” One web participant commented on chemical hypersensitivity.
• Some participants described **orthostatic intolerance and symptoms related to blood pressure drops**, including dizziness, spatial disorientation, losing balance, fainting, and falling. One participant said that numerous falls have resulted in the need for multiple back and knee surgeries.

• Some participants reported a variety of **gastrointestinal symptoms**, including irritable bowel syndrome, which as one participant described, “can flare up in reaction to activity and crashes.”

• A few participants described **depression, fear, and anxiety**, not as a symptom, but as a consequence of the devastating impact of the disease and its symptoms. As one web participant stated, “anxiety is NOT a symptom – anxiety is a byproduct [of this disease].”

• **Other symptoms** mentioned by web and in-person participants included muscle weakness, increased heart rate, immune problems, blurred vision and eyesight problems, seizures, ataxia, fevers and chills, weight loss, tinnitus, ulcers, and rashes.

**Post-exertional malaise or crashes**

The cognitive and physical symptoms of CFS and ME summarized above were described by participants as being daily realities of their disease, varying in degrees from person to person and from day to day. However, it was their collective experience with acute, debilitating PEM, which participants called a “crash” or “collapse,” that received the most attention at the meeting. As one participant said, “The term, ‘malaise’ to the lay-person is a misnomer, it is much more like a collapse.” Participants described a crash as an exacerbation of all symptoms to extreme levels that generally lead to complete incapacitation. Participants described their complete exhaustion, inability to get out of bed to eat, intense physical pain (including muscle soreness), incoherency, blacking out and memory loss, and flu-like symptoms (i.e., sore throat, congestive cough, and others). For example, two participants described their crashes in this way:

• “When people talk about being bedbound, I mean, we’re like bricks, we can’t be moved. My wife would come in and check on me to see if I was breathing because I would sleep for days at a time. I didn’t get up to eat, I didn’t get up to go to the rest room.”

• “[A crash is] not just the physical pain or it’s not just the head pain, it’s also more cognitive impairment, more orthostatic intolerance, more neurological issues…they’re very interrelated.”

Participants described how the sudden onset of crashes has put them in dangerous situations, including falling, driving in the wrong direction, unknowingly wandering across a busy street, other instances of extreme confusion in public places, and blacking out.

The FDA facilitator and panel asked several follow-up questions to probe for a better understanding of patients’ experiences with crashes.

• Many participants also seemed to agree that there are **two distinct types of crashes: physical and cognitive**. When talking about crashes associated with too much mental exertion, participants mentioned nausea, neck pain, headaches and generally being “wiped out”; as one participant said, “my head feels like it’s going to explode...and I really have to have total silence,
“total darkness.” In contrast, participants associated too much physical exertion with “whole body throbbing” that they associated with muscle pain and inflammation; as one participant said, “like if you had run a marathon.... I can barely put one foot in front of the other, barely lift my arm, I jerk.”

- Participants described the unpredictability of crashes and the fear that many patients live with every day, not knowing when or where a crash will strike. Many participants indicated, through a show of hands, that a crash can occur without warning. Some reported that crashes occurred after only mild or even no exertion, or after “something that you can normally undertake.” One participant commented that research has found that “people can crash within a few minutes of an activity or even days after, and it’s like a moving target.”

- Although they stressed the unpredictability of crashes, meeting and web participants shared their thoughts on possible triggers, including a lack of or poor quality sleep, and viral or bacterial infection stress or other situational triggers, weather or barometric pressure changes, and deep massage. A few noted that sore throat, sometimes accompanied by fever, were often associated with their crashes. One participant mentioned that her doctor correlates her crashes with very low natural killer cell function and very high viral titers. One web participant commented that “a smaller trigger can often create a smaller crash, but lots of smaller triggers can build up over time and cause a bigger crash.”

- A few participants described the “instantaneous knowledge” that a crash is about to occur. As one stated, “literally, it’s an eye movement, like I’m looking here, I look over there and, boom, I know I’m going to have a crash because I can feel my whole body changing.” A web participant commented that a crash “starts with a sound in my ear, and then my body loses strength.”

- Participants described the wide variation in the duration of crashes, from days, to weeks, to months, to even years of ongoing episodes. Patients noted that a crash can occur within minutes of overexertion (physical or mental) or as long as days after exertion. They commented that duration and intensity of activity levels that precipitate a crash do not seem to correlate to the length or magnitude of the ensuing crash.

- A few participants described how they have attempted to control their crashes, primarily through strict monitoring and activity limits. As one participant described: “when I finish a workweek.... I spend the entire day Saturday in the midst of recovery and fog and pain and exhaustion. And fortunately that recharges my nervous system enough so when I wake up Sunday, I often feel completely normal.” This participant acknowledged, however, that this 1-day recharge may not be possible for people who have a more severe form of the condition.

- Other issues raised during discussion: With regard to both cognitive and physical symptoms, a few participants commented on the cyclical nature of their conditions. For instance, one participant noted cycles as “a period of 4 to 8 weeks [with symptoms], followed by relatively good periods.” A few commented, however, that they have experienced a steady decline in their health.

- A few participants commented on the need to better understand the underlying cause of their condition. For example, one participant commented that “there is probably a single underlying
thing that is happening to all of us patients that we have not yet identified.” A few stressed the importance of focusing on what is measureable, such as natural killer cell function and viral titers.

Overall impact of CFS and ME on daily life

Participants shared a variety of experiences regarding the impact of CFS and ME on daily life, including the following:

- The expectation and “legitimate fear” of what happens when we overexert ourselves” knowing that “you will pay for it.” As one participant stressed “The patients who are [participating in this public meeting] today are generally speaking at a great cost.”

- Severe limitations with personal and household management. For example, one participant said she has to “pay to have groceries delivered, laundry washed, and my home cleaned.”

- Losing their careers, having to go on disability, or having to take new jobs with much lower levels of stress and responsibility, and being unable to pursue higher education.

- Being predominantly housebound due to their lack of energy, inability to tolerate sensory stimulation, and fear of a crash.

- Having great difficulty making plans, as they don’t know from day-to-day how they will be able to function.

- Decreased social interaction and increased isolation. Participants described no longer being able to engage in enjoyable activities such as reading books, swimming…and spending quality time with their family. As one participant commented, “My world got smaller and smaller.”

- The impact of their disease on their family. As one stated, “The worst part of this condition, for me, is the toll this disease takes on my family…I have no energy after work for anything else.”

- Experiencing harsh financial difficulties as a result of decreased or lost employment income or the high cost of treatment, often due to unapproved treatments not covered by insurance.

- Having deep personal feelings of hopelessness, emptiness, and despair. As one participant commented, “All my work and career plans went down the drain. I think I’m just waiting my turn for heaven.” A patient representative shared this experience of another, “I’m living a life of lowered expectation and I feel like this is a living death.”

Discussion Topic 2: Patient Perspective on Treating CFS and ME

The second discussion topic focused on patients’ experiences with prescription, non-prescription, and non-drug therapies used to treat their CFS and ME. Participants shared their experiences with a wide variety of treatments they are currently using or have tried. A list of all therapies mentioned during this meeting is included in Appendix 4.
Five panelists provided comments to start the dialogue. Panelists included four people living with CFS and ME and one mother of a young adult living with CFS and ME. Their comments were striking as to the range of therapies used, which included off-label uses of FDA-approved prescription drugs, experimental drugs, dietary supplements, dietary modifications, over-the-counter drugs, and non-drug therapies, such as Graded Exercise Therapy and Cognitive Behavioral Therapy. In the large-group facilitated discussion, nearly all patients and patient representatives in the audience indicated by a show of hands that their experiences were reflected in the comments shared by the panelists. Participants’ discussion on the range of treatments, their effectiveness and their downsides is described in more detail below.

Range and effectiveness of treatments

In the large-group facilitated discussion that followed the panel presentations, treatments were discussed in two broad categories. The first category was the set of therapies intended to treat the underlying cause of the disease, including immunomodulators, antivirals, and antibiotics. The second category was the wide range of therapies targeting specific symptoms of the condition. Symptomatic treatments most frequently mentioned included those for sleeplessness, enhanced alertness, unrefreshing sleep, pain, orthostatic intolerance, gastrointestinal problems, heart rate, and blood pressure. Participants reported widely varying levels of efficacy for the same treatments.

- The treatment most commented upon was the experimental drug therapy Ampligen (rintatolimod). Some participants described dramatic improvements in their physical and cognitive symptoms with their use of Ampligen, calling it “a miracle drug.” One described using Ampligen for three periods in her life; each time she started, she experienced dramatic improvement, and each time she stopped, she eventually reversed to the full devastating impact of the disease. Participants also acknowledged that Ampligen does not work for all patients.

- Participants provided varying accounts of the effectiveness of antiviral or antibiotic medications or medications targeting their immune system. A few participants described how specific treatments, often taken in combination, were very effective and “led to an amazing increase in [the] ability to get around.” Others, however, described how specific treatments were not effective for them.

- Participants commented on various medications and other therapies targeting their specific symptoms relating to pain, fatigue, and sleep dysfunction, all with varying degrees of success. Participants described a complex process of trial and error to find an effective regimen to fit their specific needs, particularly with respect to pain management. They described giving a drug enough time to see if it works, for a period of months, unless the side effects are not tolerable.

- Non-drug therapies were also raised, including yoga, stretching and relaxation techniques, and mental exercises. One participant who had not responded well to drug treatment noted that pacing (a structured method of moderating activity to avoid overexertion) is “the number one most effective strategy, without which I would never have been able to go back to work.” Participants cautioned that therapies involving physical activity were not right for everyone and must be carefully monitored by knowledgeable professionals.
• A few participants commented on the benefit of intravenous (I.V.) saline. One participant related a story in which upon experiencing a sudden onset of a crash and fainting while traveling, a doctor “gave me the saline drip, and I got up and went shopping.”

• Participants described how they have adapted in other ways, including continually monitoring their anaerobic threshold with a heart rate monitor or using activity monitors to track their activity levels. Others commented on how they “reserve energy” by using mobility aids, handicap stickers, shower chairs, and making changes to their schedules.

• In addition to treatments mentioned, participants discussed a wide range of diagnostic tools and biomarkers that clinicians have used to help treat their condition. These include natural killer cells, inflammatory cytokines, viral titers, and VO2 Max.

• Some participants who experienced even marginal effects from treatment noted that even small improvements could be significant in terms of quality of life. As one caretaker described: “[My son can now] engage in an hour of activity every other day instead of every fourth day...healthy people in this room would barely notice or think it was important at all...to him, it’s like a miracle.” Another commented, “Although I am not as well as I would like to be, these treatments have restored a great deal of purpose and meaning to my life.”

Treatment downsides

• Many participants described the significant impact of the side effects or drug interactions of their medications, especially when taken concomitantly and over a long term. For example, participants described how opioids used to treat pain exacerbate their fatigue, create “brain fog,” and gastrointestinal issues, and risk of addiction. Others mentioned stomach and esophageal problems with anti-inflammatories, sleepwalking-type issues with Ambien, jitters and high pulse rates from Adderall, as examples.

• Some participants commented that their therapies had good initial success, sometimes for long periods of time, but then became less effective over time or as the disease progressed or flared. As one commented, “I've probably tried at least 25 drugs [for pain], maybe more, and over time they lose effectiveness. I have to switch it up.”

• Some participants expressed frustration with their access to treatment options. A few described moving across the country to obtain treatment. One participant stressed that a lot of specialized treatments “are limited to a very small population of CFS patients” who have enough insurance, money, knowledge, and family support to obtain them. A few described experiences with health care professionals who did not take their disease seriously or refused to treat it.

• A few expressed concern that their treatments focus on the symptoms, not the root cause.

• A few participants commented that if not handled carefully, symptomatic treatments can mask symptoms and make it difficult for patients to monitor or control their activity levels and avoid the overexertion that leads to a crash.
• A few participants commented on the financial cost of treatment, particularly the out-of-pocket cost for experimental or other unapproved treatments not covered by their insurance. As one participant noted, “My medical expenses can be as much as $2,500 per month.”

Other issues raised in the discussion:

• A few participants stated their belief that there is a variety of subsets or subtypes of people affected with CFS and ME. They pointed to the variability in how treatments work for some, but not others. One web participant urged identification of subtypes “so that we don’t hurt ourselves by trying [drugs that don’t work for us].”

• A few participants stressed that they or their loved ones would be willing to accept significant risk for the opportunity to try new treatments to potentially alleviate or cure their condition. One web participant, however, commented that “I am quite wary of [taking risks]. I'm very unwell, but I know how to manage at this level. Trying a new medication has typically caused side-effects that take me weeks or months to recover from.”

Summary of Comments Submitted to the Public Docket

More than 220 comments were submitted to the public docket that supplemented the April 25 Patient-Focused Drug Development meeting. The majority of comments were submitted by patients or caretakers. Several comments contained photos or links to videos. The docket also included reports of the two surveys conducted by patient representatives, which were mentioned at the meeting. They are here referred to as the CFIDS survey and the Chu and Jason survey.

The comments largely supported the perspectives shared by participants at the April 25 meeting. They also provided rich context to support the meeting input. The following is a summary of comments provided through the docket on CFS and ME symptoms, impacts, and current treatments. Particular focus is placed on experiences or perspectives not addressed in detail at the meeting.

Submitted comments on symptoms of CFS and ME

The submitted comments reiterated that CFS and ME is a complex multi-system disease associated with a wide range of debilitating and often interrelated symptoms. Over 50 different symptoms of the disease were mentioned in the docket comments. Each of the following symptoms was raised by over 40 commenters: cognitive impairment, severe fatigue or exhaustion; unrefreshing sleep or sleep disturbances; orthostatic intolerance, dizziness, or other issues related to blood pressure drops; headaches or migraines; muscle pain; other pain; sensitivity to light, sound, temperature, or odors; and gastrointestinal issues. The results of the two submitted surveys also appear to be consistent with the input from the meeting and submitted comments.

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6 See footnote 5.
7 Because this report centers on CFS and ME symptoms, impacts, and patients’ treatment approaches, comments pertaining to these topics are the focus of this report. The comments to the docket covered a wide range of other important topics related to drug development for CFS and ME, such as disease definition, repurposing treatments, outcome measures, and regulatory issues. Comments on these topics were also reviewed and considered by FDA.
Below are highlights of a selection of frequently mentioned symptoms.

- **Impairments to cognitive functioning**, in various forms, were the most frequently mentioned symptoms. Comments reiterated a key theme of the April 25 meeting: that the effects on cognitive functioning are as significant to patients as their physical symptoms. Consistent with the meeting, commenters described an “inability to concentrate,” “episodes of confusion,” “difficulty finding words,” “lack of judgment,” and “brain fog that stops me dead in the middle of a thought.” A few described various impairments to memory, for example “forgetting how to spell common words” and “inability to recall basic facts.”

- **Debilitating fatigue, exhaustion, and weakness** was one of the most cited set of symptoms in the comments and in the two submitted surveys. Commenters provided concrete examples of living with “bone-crushing” or “unimaginable fatigue and extreme exhaustion.” Some of the more extreme examples included: “too exhausted to change clothes more than every 7-10 days”; “exhaustion to the point that speaking is not possible”; “exertion of daily toileting, particularly bowel movements, sends me back to bed struggling for breath and feeling like I just climbed a mountain.” A few described a “tired but wired” feeling.

- **PEM, crashes or “repeated severe relapses” after even minimal exertion** were commonly described in the submitted comments. As one said, “The [overexertion] is a low threshold that normally can’t be sensed at the time...the crash usually comes the next day.” Like the meeting participants, commenters associated a crash with an incapacitating exacerbation of all symptoms, particularly, exhaustion, flu-like symptoms, muscle aches, and cognitive impairment.

- Problems related to **sleep dysfunction**, including insomnia, sleep disruptions (staying asleep) and “non-restorative” or “unrefreshing sleep,” were among the most commonly cited symptoms in the submitted comments.

- **Headache or migraines** were the most frequently cited specific types of pain and one of the most commonly mentioned symptoms of CFS and ME. Commenters described “daily migraines,” “headaches with nausea,” “full-body ice cream headache-like pains,” and feeling like “my brain was going to explode.” **Muscle or joint pain** was also among the most cited specific types of pain in the comments, with one commenter noting, “My muscles constantly burn.”

- Although not discussed in detail at the April 25 meeting, **susceptibility to infection** was frequently mentioned in the submitted comments. Specific viral or other infections mentioned included human herpes virus or HHV-6 or chronic herpes, Epstein-Barr Virus or EBV, varicella zoster virus or shingles, candida, pneumonia, urinary tract infection, and others. Many also commented that test results have shown abnormally “low natural killer cell function,” “elevated cytokines,” “elevated RNAse activity,” and “low T4 helper cell counts,” among others.

- Although not discussed at the April 25 meeting, **temperature intolerance** or the “inability to regulate temperature,” including “night sweats,” was frequently raised in the submitted comments. In the CFIDS survey, “heat intolerance” and “cold intolerance” were both among the ten most frequent phrases used to describe symptoms, and almost 60% of respondents in the Chu and Jason survey cited “temperature intolerance” as a “major” symptom.
Many other CFS and ME symptoms or concomitant conditions were identified in the comments, but not discussed in detail at the April 25 meeting. These included anemia, angina and other heart conditions, asthma, burning skin, emotional over-reactivity, endometriosis, endocrine problems, enlarged lymph nodes, hives, muscle tremors, poor oxygen consumption, reduced fine motor skills, respiratory problems, restless leg syndrome, signs of stroke, and others.

Submitted comments on patients’ ability to perform specific activities

More than 99% of respondents to the Chu and Jason survey indicated that CFS and ME has affected social/family activities, household tasks, and work/school activities; 89% indicated that the illness has affected their personal care activities. These survey results appear to be consistent with the submitted comments, which provide concrete examples of how patients’ symptoms or their fear of a crash has significantly limited their ability to do activities that are important to them:

- Most described limits to physical activities, including showering once every five days; not walking up a flight of stairs; or “not being able to carry a half a bag of groceries.”

- Many described limits to more social or cognitive activities, such as not being able to be on the computer, or not being able to help their children with homework. For example, one commenter stated: “There were days when I couldn’t even remember...how to answer a simple multi-line phone and transfer a call within the office.”

- Some described an overall reduction in their activity level, generally speaking. A few estimated that, overall they “operate at about 20%, 25%, or 30% of normal.”

- Some described an inability to participate in many activities because of their intolerances to light, sound, and other stimuli, including listening to music, watching TV, going on the internet, participating in conversations, being outdoors, etc.

- A few described how their inability to be active further exacerbates their weakness, fatigue, and pain and causes them “to become even more debilitated.”

- A few described being regularly or completely bedbound, unable to eat, “speak above a whisper,” or even think.

Submitted comments on the best days versus worst days with CFS and ME

Some commenters described how the disease affects their daily life on best days versus worst days. The descriptions of best days varied but generally included having relief from headaches, muscle pain, and flu-like symptoms and having the ability to “be out of bed for up to two hours, take care of personal needs without relying on assistance, do basic household chores, go out for small errands, care for their children, and engage in limited social interaction.” A few said that even on their best days, they must lie down most of the time and use mobility aids. Those who commented on their worst days described severe pain and weakness, being confined to bed, requiring complete quiet and darkness, and requiring assistance or being unable to engage in any personal care, household care, or social interaction.
The results of the Chu and Jason survey support these descriptions. Over 70% of respondents reported that on their best days, they “can do light housework” or “can only work part-time or on some household tasks” while 19% reported that they can only “walk around the house” and 3% reported being “bedridden.” Conversely, only 6% of respondents reported on their worst days, they “can do light housework” or “can only work part-time or on some household tasks,” while 32% reported that they can only “walk around the house” and 61% reported being “bedridden.”

Submitted comments on the overall impact of CFS and ME on patients’ lives

The docket comments also reiterated the devastating impact that CFS and ME has on patients’ ability to take care of themselves and their families and sustain their careers, their financial independence, and their relationships. Their descriptions of the toll that CFS and ME has had on their lives largely reflects the input received in the meeting. Many commenters described having to give up their professional careers or their academics, and almost 75% of respondents to the Chu and Jason survey reported being on “disability due to CFS or ME” or “unemployed due to CFS or ME.” Some described being completely housebound or even bedbound and requiring assistance with daily activities.

Commentators also described the toll the disease has on their mental and emotional well-being, including increased fear and anxiety, social isolation, “a narrow life,” and changes to self-identity. As one commented, “I’ve had to rethink who I am.” Some expressed feelings of hopelessness and despair—that the disease has “stolen” their lives.

Submitted comments on current treatments for CFS and ME

The submitted comments reiterated the wide range of treatments that are currently used to address either the underlying cause(s) of CFS and ME or to manage the many symptoms of the disease. Over 150 specific medications and non-drug therapies were identified in the submitted comments. Many of the treatments were mentioned in the meeting, but an even greater number was not discussed at the meeting. Only a small number of therapies were mentioned by more than ten comments in the docket. The more commonly mentioned therapies included (in alphabetical order): Ampligen, dietary restrictions, gamma globulins or IVIG, Klonopin (clonazepam), pacing, supplements, Valcyte, and others. The set of medications and non-drug therapies identified at the meeting or through the docket comments is listed in Appendix 4. Key themes regarding current treatments include the following:

- Many commenters described more effectively managing their disease through non-drug therapies, especially by placing strict control over their diet, their activities, and their environment. They described “pacing,” “staying within my energy envelope,” “staying away from stressful situations,” and “listening to my body.” In the CFIDS survey, five of the top ten phrases used to describe treatments were “vitamins,” “diet,” “nutritional supplements,” “fish oil,” and “acupuncture.” In the Chu and Jason survey, pacing was the most frequently tried treatment, and over 70% of respondents who identified pacing rated it “effective.”

- Consistent with the meeting, the comments reflected the wide variability in effectiveness of various treatments. Specific treatments identified by some commenters to “work for them” were identified by others as either not working or worsening their health. A few described “fleeting improvement, but it never lasts long.” Over 70% of respondents to the Chu and Jason
survey reported that overall, their current treatments are either “not helpful” or “slightly helpful.”

- Areas identified as **not being adequately addressed by current therapies** included orthostatic intolerance, pain, exhaustion, sleep management, cognitive impairment, immune system, and treating the underlying cause(s).

- The comments echoed the various **treatment downsides** identified at the meeting, and they included many examples of “bad reactions,” negative impacts on “brain function,” treatment access issues, etc.

- The comments also reiterated the **complex process of trial and error** to find effective and tolerable treatments and the reality that treatments may lose their effectiveness over time. A few described having “tried hundreds of drugs.”

- The patients and other patient representatives who submitted comments were united in their belief in the **need for targeted and effective treatments** to treat the underlying cause(s) and symptoms of this devastating disease.

**Conclusion**

FDA is grateful to patients, caretakers, and others who so thoughtfully and courageously shared their experiences and perspectives on CFS and ME through the Patient-Focused Drug Development initiative. It is clear that CFS and ME is a debilitating disease that can severely affect a patient’s day-to-day functioning and have a devastating impact on a patient’s life. The variability in the nature of symptoms and in the approaches to treatment is striking. Patients have tried a wide range of drug and non-drug therapies with varying effectiveness, and for some, none are effective.

This meeting was the first of the Patient-Focused Drug Development meetings. It allowed FDA to obtain patients’ point of view, in a systematic way, on the severity of CFS and ME, its impact on daily life, and available treatment options. FDA recognizes that patients have a very unique ability to contribute to our understanding of this broader context of the disease, which is important to our role, and that of others, in the drug development process. We share the patient community’s commitment to facilitate the development of safe and effective drug therapies for this disease.
Appendix 1: Discussion Questions

Topic 1: Disease Symptoms and Daily Impacts That Matter Most to Patients

1. What are the most significant symptoms that you experience resulting from your condition? (Examples may include prolonged exhaustion, confusion, muscle pain, heat or cold intolerance.)

2. What are the most negative impacts on your daily life that result from your condition and its symptoms? (Examples may include difficulty with specific activities, such as sleeping through the night.)
   a. How does the condition affect your daily life on the best days and worst days?
   b. What changes have you had to make in your life because of your condition?

Topic 2: Patients’ Perspectives on Current Approaches To Treating CFS and ME

1. What treatments are you currently using to help treat your condition or its symptoms? (Examples may include FDA-approved medicines, over-the-counter products, and other therapies, including non-drug therapies such as activity limitations.)
   a. What specific symptoms do your treatments address?
   b. How has your treatment regimen changed over time and why?

2. How well does your current treatment regimen treat the most significant symptoms of your disease?
   a. Have these treatments improved your daily life (for example, improving your ability to do specific activities)? Please explain.
   b. How well have these treatments worked for you as your condition has changed over time?
   c. What are the most significant downsides of these treatments (for example, specific side effects)?
Appendix 2: Patient and FDA Panel Participants

Patient Panel 1

- Jon Kaiser – Patient
- Joseph Landson – Patient
- Denise Lopez-Majano – Caregiver
- Kim McCleary – representing CFIDS Association of America
- Charlotte von Salis – Patient

Patient Panel 2

- Mary Dimmock – Caregiver
- Natasha Kelemen – Patient
- Matina Nicholson – Patient
- Mary Schweitzer – Patient
- Amanda Simpson – Patient

FDA Panel

- Laurie Burke, Office of New Drugs, CDER
- Sandra Kweder, Office of New Drugs, CDER
- Theresa Michele, Office of New Drugs, CDER
- Theresa Mullin, Office of Strategic Programs, CDER
- Theresa Toigo, Office of the Center Director, CDER
Appendix 3: Incorporating Patient Input into a Benefit-Risk Assessment Framework for CFS and ME

Introduction

Over the past several years, FDA has developed an enhanced structured approach to benefit-risk assessment in regulatory decision-making for human drugs and biologics. The Benefit-Risk Assessment Framework involves assessing five key decision factors: Analysis of Condition, Current Treatment Options, Benefit, Risk, and Risk Management. When completed for a particular product, the Framework provides a succinct summary of each decision factor and explains FDA’s rationale for its regulatory decision.

In the Framework, the Analysis of Condition and Current Treatment Options rows summarize and assess the severity of the condition and therapies available to treat the condition. The assessment provides an important context for drug regulatory decision-making, including valuable information for weighing the specific benefits and risks of a particular medical product under review.

The input provided by patients and patient representatives through the CFS and ME Patient-Focused Drug Development meeting and docket comments will inform our understanding of the Analysis of Condition and Current Treatment Options for this disease.

The information in the top two rows of the sample framework for CFS and ME below draws from various sources, including what was discussed at the CFS and ME Patient-Focused Drug Development meeting held on April 25, 2013. This sample framework contains the kind of information that we anticipate could be included in a framework completed for a drug under review for CFS and ME. This information is likely to be added to or changed over time based on a further understanding of the condition or changes in the treatment armamentarium.

Sample ME-CFS Benefit-Risk Assessment Framework

<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
</table>
| Analysis of Condition | – CFS and ME is a chronic multi-system disorder characterized by profound fatigue lasting for six or more months that is not improved by bed rest and that may be worsened by physical or mental activity. The disease may occur with a sudden or gradual onset.  
– Symptoms often include impaired cognitive functioning, severe fatigue or exhaustion, | CFS and ME is a serious disease. It is a highly variable disease and may manifest in different ways from person to person. It severely affects day-to-day functioning, and some patients struggle with the simplest tasks of daily life. CFS and ME has had devastating effects on many patients’ lives. |

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8 Commitments in the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) include further development and implementation of the Framework into FDA’s review process. Section 905 of the FDA Safety and Innovation Act also requires FDA to implement a structured benefit-risk framework in the new drug approval process. For more information on FDA’s benefit-risk efforts, refer to [http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm](http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm).
<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
</table>
| unrefreshing sleep, chronic pain, tender lymph nodes, sore throat, orthostatic intolerance, and sensory sensitivities. The nature and severity of symptoms vary from person to person. Many patients experience post-exertional malaise or a crash, which may occur without warning and upon even minimal physical or cognitive exertion and is associated with an acute exacerbation of these symptoms.  
- For most, CFS and ME affects their ability to function in daily activities of work, school, household management, and personal care. Many are bedbound some or all of the time. Many experience loss of careers, decreased quality of family life, social isolation, and feelings of hopelessness.  
- It is estimated that 1 to 4 million people in the US are afflicted with CFS and ME.  
- Refer to the Voice of the Patient report for a more detailed narrative. | |
| Current Treatment Options | - There are no FDA-approved therapies for this condition.  
- Various off-label prescription and non-prescription drug therapies are used by practitioners and patients. Therapies used to treat the underlying disease often include immunomodulators, antivirals, and antibiotics. A wide variety of drug therapies are also used to treat the symptoms of the disease, including analgesics, antidepressants, anti-inflammatory, beta blockers, muscle relaxants, opioids, sedatives, and stimulants.  
- Non-drug therapies such as pacing, exercise plans, dietary restrictions, vitamins, and supplements are common.  
- Many patients have experimented with a multitude of complex treatment regimens, with varying degrees of success.  
- Refer to the Voice of the Patient report for a more detailed narrative. | A significant unmet medical need exists for patients with CFS and ME. Many patients have tried a wide range of drug and non-drug therapies, and for some, none is effective. Patients are desperate for a treatments that target the underlying cause of the disease. |
Appendix 4: Table of Treatments Discussed by Patients

The table below lists various drug and non-drug treatments and other terms mentioned by participants during the April 25 Patient-Focused Drug Development meeting or in comments submitted to the public docket. The treatments are grouped according to the treatment type or targeted symptom implied in the comments (when identification is possible).

**Note:** The purpose of this table is to illustrate the range of treatments as described by CFS and ME patients. This list may not include all treatments mentioned. Since there are no FDA-approved drugs indicated to treat patients with CFS and ME, FDA-approved products mentioned would have been used off-label. This list also includes products that are not approved by FDA.

Inclusion in this table does not represent endorsement by FDA.

<table>
<thead>
<tr>
<th>Drug Therapies</th>
<th>Treatment type or targeted symptom</th>
<th>Specific treatment mentioned (in no particular order)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alertness, Memory, Cognitive Function</strong></td>
<td></td>
<td>Adderall, Provigil, Vyvanse, Valcyte, Namenda, other unspecified stimulants</td>
</tr>
<tr>
<td><strong>Angina</strong></td>
<td></td>
<td>Beta blockers, nitrates, Apo Diltiaz</td>
</tr>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
<td>fluconazole</td>
</tr>
<tr>
<td><strong>Antiviral, antibiotic or immunomodulator</strong></td>
<td></td>
<td>Ampligen, famciclovir, Valtrex, Valcyte, cidofovir, azithromycin, doxycycline, amantadine, Levaquin, Ceftin, amoxicillin, Suprax, acyclovir, ganciclovir, vaccine for staph</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
<td>buspirone</td>
</tr>
<tr>
<td><strong>Auto-immune</strong></td>
<td></td>
<td>rituximab, Imunovir, gamma globulins (including intravenous immunoglobulin or IVIG), Kineret, naltrexone</td>
</tr>
<tr>
<td><strong>Breathing difficulties</strong></td>
<td></td>
<td>Advair, Budesonide</td>
</tr>
<tr>
<td><strong>Crash symptoms</strong></td>
<td></td>
<td>I.V. saline</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td></td>
<td>Prozac, Pamelo, Desyrel, Wellbutrin, other unspecified antidepressants</td>
</tr>
<tr>
<td><strong>GI issues</strong></td>
<td></td>
<td>Omeprazole, hyoscyamine</td>
</tr>
<tr>
<td><strong>Heart Rate / Blood pressure</strong></td>
<td></td>
<td>Bystolic, ditiazem, metoprolol, Travatan (for eye pressure)</td>
</tr>
<tr>
<td><strong>“help bolster my immune system”</strong></td>
<td></td>
<td>Hepapressin, Nexavir</td>
</tr>
<tr>
<td><strong>Hives</strong></td>
<td></td>
<td>Benadryl</td>
</tr>
<tr>
<td><strong>Hypothyroidism, thyroid problems</strong></td>
<td></td>
<td>Cytomel, levothyroxine</td>
</tr>
<tr>
<td><strong>“Increase energy levels”</strong></td>
<td></td>
<td>Savella</td>
</tr>
<tr>
<td><strong>Joint inflammation</strong></td>
<td></td>
<td>Meriva</td>
</tr>
<tr>
<td><strong>Muscle relaxation</strong></td>
<td></td>
<td>Tizanidine, Skelaxin, cyclobenzaprine</td>
</tr>
<tr>
<td><strong>Orthostatic intolerance / neurally mediated hypotension (NMH) / Postural orthostatic tachycardia syndrome (POTS)</strong></td>
<td>I.V. saline, atenolol, propranolol, pindolol, midodrine, Florinef, pyridostigmine</td>
<td></td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td>Cymbalta, Savella, Lyrica, Flexeril, gabapentin, Vicodin and other unspecified opioids, Advil (ibuprofen), Voltaren gel and other topicals, low dose naltraxone, topical compound (ingredients stated as: Neurontin (gabapentin), lidocaine, diclofenac, cyclobenzaprine, baclofen), combination product (Topamax, tricylic antidepressants, Ultram, lorazepam), Darvocet, Tylenol (acetaminophen), Duragesic, clonazepam, trazodone, sumatriptan, diclofenac, amlopidine, dicyclomine, promethazine, bumetamide, Mirapex, butalbital, piroxicam, nortriptyline, Percocet, aspirin, Excedrin</td>
</tr>
<tr>
<td>Treatment type or targeted symptom</td>
<td>Specific treatment mentioned (in no particular order)</td>
<td></td>
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<tr>
<td>------------------------------------------------------------------------</td>
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<td></td>
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<tr>
<td>Restless leg syndrome</td>
<td>carbidopa/levadopa</td>
<td></td>
</tr>
<tr>
<td>Sleep management, unrefreshing sleep</td>
<td>Ambien (zolpidem), Flexeril, Klonopin (clonazepam), mirtazepine, Soma, other unspecified sleep medications, amitriptyline, Xanax</td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td>anti-inflammatory (specific types not mentioned)</td>
<td></td>
</tr>
<tr>
<td>Other or no specific symptoms mentioned</td>
<td>levothyroxine, levcarnitine, nabumetone, fluticasone, albuterol, ondansetron, doxepin, antihistamine, naproxen, IV amino acids, Xyrem, Lamictal, cholestyramine, anti/protozoals, Prosom, insulin, Terazol, Sinemit, L Dopa, meloxicam, temazepam, cyanocobalamin, Zoloft, amphetamines, baclofen, lorazepam</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-drug therapies mentioned (in no particular order)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplements and Diet</td>
<td>B12 injections, Super B Complex, GcMAF (Gc protein-derived macrophage activating factor), Myer’s Cocktail, ImmunoProp, ImmunoProp Plus, equilibrate, glutathione, Vitamin C, Vitamin D, Vitamin E, levo-carnitine, multivitamin, resveratrol, melatonin, coral calcium, folate, fish oil, flax oil, DHEA, Cellfood, Neuro-chord CaMg+, Fibermucil, olive leaf extract, Augmentin, Equilibrant, Armour thyroid, CoQ10, gastrolyte, antioxidants, probiotics, non-specified vitamins; avoid or eliminate: sugar, coffee, alcohol, aspartame, processed foods; drink 80-100 ounces of water per day, Super-Immunity Diet, other unspecified dietary changes</td>
</tr>
<tr>
<td>Non-drug therapies</td>
<td>Pacing, activity program, sleep hygiene, Graded Exercise Therapy (GET), physical therapy, Feldenkrais method, Cognitive Behavioral Therapy (CBT), transcutaneous electrical nerve stimulation (TENS), heating pad, acupuncture, chiropractic, Lumosity, herbs/herbal treatments, massage, meditation, infrared sauna, oxygen therapy, chelation therapy, medical marijuana, Marshall Protocol, osteopathy, compression stockings</td>
</tr>
</tbody>
</table>