

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

Fibromyalgia

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Center for Drug Evaluation and Research (CDER)
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Introduction

On March 26, 2014, FDA held a public meeting to hear perspectives from people living with fibromyalgia about their disease, its impact on their daily life, and currently available 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 a five-year period, 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>.

Overview of Fibromyalgia

Fibromyalgia, also known as fibromyalgia syndrome, is a chronic condition that affects approximately five million adults in the United States. Women are disproportionately affected, making up about 80-90% of those diagnosed. The condition is primarily characterized by chronic, widespread pain in the body's muscle and soft tissues. Other common symptoms include chronic fatigue, sleeping difficulties, cognitive issues, depression, and gastrointestinal issues. Symptoms vary among patients, and they can improve or worsen over the course of time.

Many patients develop a custom treatment regimen aimed at treating the symptoms that impact them most. There are three drug treatments approved for managing pain and other fibromyalgia symptoms: Lyrica (pregabalin), Cymbalta (duloxetine), and Savella (milnacipran). Other prescription drugs used (off-label) to treat patients with fibromyalgia include pain relievers, sleep aids, anticonvulsants, antidepressants, and muscle relaxants. Non-drug therapies and lifestyle modifications, such as diet and exercise, physical therapy, massage, heat and ice, acupuncture, and limiting activity are also used to help manage symptoms.

Meeting overview

This meeting provided FDA the opportunity to hear directly from patients, caretakers, and advocates about their perspectives on fibromyalgia and its treatments. 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 fibromyalgia. The questions for discussion (*Appendix 1*) were published in a [Federal Register notice](#) that announced the meeting. For each topic, a panel of patients (*Appendix 2*) shared comments to begin the dialogue. Panel comments were followed by a facilitated discussion inviting comments from other patients and patient representatives in the audience. The discussion was led by an FDA facilitator, and a panel of FDA staff (*Appendix 2*) asked follow-up questions. Participants who joined the meeting via live webcast were invited to submit comments throughout the discussion. Additionally, in-person and web participants were periodically invited to respond to polling questions (*Appendix 3*), which provided a sense of the demographic makeup of participants and how many participants shared a particular perspective on a given topic.

Approximately 40 fibromyalgia patients or patient representatives attended the meeting in-person, and over 65 web participants provided input through the live webcast and polling questions. According to their responses to the polling questions, in-person and web participants represented a range of patients, with a higher proportion of women (nearly 90%), adults aged 31-50, and patients living with the disease for more than 20 years. Although participants may not fully represent all of the population living with fibromyalgia, FDA believes that the input received reflects a range of experiences with fibromyalgia symptoms and treatments.

To supplement the input gathered at the meeting, patients and others were encouraged to submit comments on the topic to a public docket, which was open until May 26th, 2014. Nearly 400 docket comments were submitted to the public docket,¹ the majority by individual fibromyalgia patients. FDA also received several comments from patient caregivers and fibromyalgia advocacy groups. Three of the submitted comments from advocacy organizations contained data from surveys and perspectives of fibromyalgia patients; representatives from these organizations mentioned interim analyses of these studies at the March 26 meeting.

More information on the meeting, including the archived webcast recording and meeting transcript, is available on the meeting website:

<http://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm363203.htm>

Report overview and key themes

This report summarizes the input provided by patients and patient representatives at the meeting or through the webcast. It also includes a summary of comments submitted to the public docket. To the extent possible, the terms used in this report to describe specific fibromyalgia symptoms, impacts and treatment experiences reflect the words used by in-person attendees, web participants, or docket commenters. 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 input from the meeting and docket comments underscore the chronic and debilitating effect that fibromyalgia has on patients' lives and the challenges patients face in finding effective and tolerable therapies to help manage their condition. Several key themes emerged from this meeting:

- The health effects of fibromyalgia are pervasive and wide ranging. Participants described living with daily unrelenting chronic widespread pain, persistent chronic fatigue, sleep issues, and cognitive effects, in addition to a range of other debilitating symptoms. Many shared their fears of symptoms worsening over time.
- Fibromyalgia impacts all aspects of patients' lives. Participants described severe limitations in maintaining relationships, performing at work or school, and caring for self and family. They shared the emotional toll of experiencing stigma within society, social isolation, healthcare and financial challenges of treatment, and fears of living with an often misunderstood condition.

¹ 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.

- Participants described using a combination of drug and non-drug treatments and a range of health care specialties in a multi-modal treatment approach. Many participants noted the significant burden of a trial and error therapy regimen, making difficult decisions on benefits versus adverse effects of treatments, and access issues to opioids.
- Participants emphasized the need for increased awareness and understanding of fibromyalgia across the medical community. They also emphasized the importance of identifying the underlying cause of fibromyalgia. Participants stressed the need for a holistic approach to treating fibromyalgia, including lifestyle management, diet and exercise, and psychosocial techniques, in addition to medical treatments.

The sections that follow detail the views shared by patients and patient representatives. The patient input generated through this Patient-Focused Drug Development meeting and public docket strengthens FDA's understanding of the burden of fibromyalgia on patients and the treatments currently used to treat fibromyalgia and its symptoms. FDA staff will carefully consider this input as it fulfills its role in the drug development process; including advising sponsors on their drug development programs and assessing benefit-risk for products under review for marketing approval (see Appendix 4). 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 fibromyalgia patients, for example with regards to fatigue or cognitive effects. It could also point to the potential need for development and qualification of new outcome measures in clinical trials.

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

The first discussion topic focused on patients' experiences with their fibromyalgia symptoms and the resulting effects on their daily lives. FDA was particularly interested in hearing about specific activities that patients can no longer do at all, or as fully as they would like, because of their condition.

Five panelists (Appendix 2) provided comments to start the dialogue, including four women and one man. One panelist was unable to attend the meeting in-person due to a pain flare up and presented her comments via webcast. All panelists reported having lived with symptoms for several years, including a woman diagnosed as a teenager and a man recently diagnosed with fibromyalgia. Panelists described the depth of challenges they face with a range of fibromyalgia symptoms, and the impact that their symptoms have on their ability to perform daily activities. They also described the significant frustration, stress, and fear they have experienced because of their condition. 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. Several participants mentioned that symptoms presented after some type of physical injury.

In a polling question (Appendix 3, Q7), participants were asked to identify up to three symptoms that have the greatest impact on their or their loved one's life. Chronic pain, fatigue, and difficulty concentrating or memory problems received the highest number of responses. Responding web participants reported similar results to those participating in-person. The facilitated discussion provided a look into how symptoms manifest and how they are interrelated. The range of symptoms discussed by in-person and web participants is described in more detail below.

Perspectives on most significant symptoms

Chronic Pain

The most frequently discussed symptom by in-person and web participants was chronic widespread pain that may be experienced throughout the body, or in one or more localized areas. Pain was identified in unique ways: burning or “hot stabbing,” muscle stiffness, muscle spasms, skin or nerve pain, and headaches.

Participants also described debilitating pain in joints and tender points², resulting in painful swelling and immobility. Participants shared their inability to rotate, stretch, and bend body parts without experiencing intense discomfort due to extreme muscle stiffness. Pain symptoms were described by individuals in strikingly different ways: “electrifying,” “bee stings,” “pins and needles,” and “deep bone-aching.”

The following examples illustrate the experiences shared in the discussion of pain by participants.

- “The pain is so bad, like if somebody walks across the floor, I can feel that. It feels like there are knives sticking into my body.”
- [I have] “unrelenting widespread chronic pain that won’t stay in one spot. It starts out in the morning in the neck, and then by the afternoon it’s in my lower back, and by the evening it’s in my legs and feet.”
- “Climbing a couple of stairs is agonizing. My leg muscles feel leaded, stiff, and weak, and almost as if they are going to rip if I continue to walk.”
- “Having my two-year-old granddaughter hug me hurts so much, I would like to push her away, but I don’t want to.”
- “I get like a burning pain...that you get exercising, I get that from just standing up and walking in the kitchen, or just standing there, you know, trying to cook a meal.”
- “Spasm pain...feels like my muscles contracting and just not letting go.”

Participants commented that pain can manifest in the form of chronic headaches that may also escalate to severe migraines. One participant likened his “24/7” headaches to wearing a “mold of your head that’s a quarter inch too small all the way around...just absolute crushing headache.” A few participants identified activities that could trigger headache symptoms, such as sleep problems, lifting “items that are more than half a pound,” working on the computer, vibrations from a car on bumpy roads, and constant movement of hands, arms and shoulders.

² As described by the National Institutes of Health, “Tender points are found in the soft tissue on the back of the neck, shoulders, chest, lower back, hips, shins, elbows, and knees. “

Pain flare-ups

Several participants commented on “flare-ups,” in which they experience intense pain without any warning. One participant noted, “During flares, it becomes a deep grinding pain that feels as if someone is kneading my muscles. I have bad days and good days that are mixed, never knowing when they will occur and to what extent.” Participants identified triggers leading to flare-ups, such as weather changes, intolerably high or low temperatures, stress, lack of sleep, or over-exertion of muscles. Some participants mentioned that paying attention to bodily cues helped to predict and prevent flare-ups. This method allowed participants to rest and administer therapeutic treatments that lessened the impact of the flare-up.

Chronic fatigue

Many participants identified chronic fatigue as one of the most significant symptoms of fibromyalgia impacting their daily life. About 75% of web participants also identified fatigue as one of their top three health effects. Participants described an “overwhelming feeling of tiredness that is not relieved by sleep or any rest” and feeling as if “I literally hit a brick wall...all of a sudden I come to a complete and total stop.” A few participants described periodic experiences with unpredictable, severe bouts of fatigue. One participant shared, “In a worse state I'm sleeping the majority of the day, awakening and still feeling lousy.”

Participants provided various thoughts on how fatigue manifests:

- “It manifests in burning sensations in the muscles being used...can be felt in the jaw muscles when chewing and extraocular muscles when looking around.”
- “One of the fatigue symptoms I have...what I call ‘iron muscle’. The muscles in my body will feel like they are made of iron and become heavy and lock up.”
- “[My] limbs feel large/heavy, no ability to concentrate on ANY thought, speaking aloud requires too much energy, [I] can't read, watch TV, converse, or stand.”
- “The fatigue is just so completely and totally overwhelming that it is hard to even have the energy to breathe.”

Cognitive symptoms

Cognitive symptoms were frequently described in terms of memory issues and “brain-fog” or “fibro-fog.” To illustrate, one panelist noted, “In terms of memory, I live with Post-It notes, even having to record important information that may have been told to me just moments ago.” A few participants specifically commented that cognitive issues can manifest as the inability to form spoken words. One patient described, “I can't get the word out of the mouth. I can't get the word into my brain. They may come out in a different order.” Another noted, “The more I struggle to recall words, the more distressed I become, only worsening the ability to think.” Others described cognitive issues as confusion, racing thoughts, clumsiness, “brain-disconnect” and feeling as if “my brain just leaves me.”

Other symptoms

In addition to chronic pain, chronic fatigue, and cognitive symptoms, participants described a number of other symptoms that have a significant impact on their daily lives:

- Many participants described **inconsistent sleep patterns** and **insomnia**. Participants shared their difficulties falling asleep, staying asleep, or experiencing unrefreshing sleep. Some participants noted the relationship between pain and sleep. One participant shared, “I can’t sleep at night because of the pain. And my worst position is lying down in bed.” FDA asked participants whether treating sleep issues would alleviate other fibromyalgia symptoms. Several participants agreed, with one sharing that “I found something for sleep, and my symptoms are much better.”
- A few participants commented on experiencing **sensory overload** or heightened sensitivity as a significant health effect. Some described increased reactions to hot and cold temperatures, while another shared, “I have heightened sensory modality during these times. Sounds are amplified, smell is intensified... touch and breathing are irritating against my skin.”
- Some participants described experiencing **vision problems** as a significant symptom, especially during pain flare-ups. One shared, “Where major flare-ups occur, I partially lose the use of my near sightedness, leaving me unable to read anything for hours at a time.” Vision changes, eye swelling, inability to focus, dry eye syndrome, and an increased batting of the eyes were also mentioned.
- Some participants described **orthostatic intolerance** and symptoms related to drops in blood pressure, including dizziness, feeling weak and unstable, losing balance, fainting, and falling. Those that shared their experiences noted the fainting or dizziness spells would happen without trigger or warning.
- Many in-person participants and nearly 20% of web participants commented on **anxiety and depression**, often linking it to the difficulty in living with fibromyalgia symptoms and worry about the future. One participant shared of his fibro-fog, “I start to have a panic attack because I’m alone and my mind has just given out on me, and it’s extremely scary to think that your mind has just left you.”
- **Other symptoms** included gastrointestinal issues (e.g., nausea and irritable bowel syndrome), low libido, and a variety of motor issues. These included restless leg syndrome, periodic limb movement syndrome, erratic movements, and eyelid and muscle twitching. One web participant described her motor issues as, “the more I walk, the tighter my legs get and the more painful it is.”
- A range of **comorbid conditions** were identified during the meeting, including osteoarthritis, metabolic syndrome, polycystic ovarian syndrome, delayed sleep phase syndrome, hypo- or hyper-active thyroid and Vitamin D deficiency.

Overall impact of fibromyalgia on daily life

Both in-person and web participants described in rich detail the impact that their condition has on daily life, including:

- **Worry about the future.** One panelist worried about reaching “the point of becoming wheelchair bound or bed ridden...my worst fear is having to live the rest of my life this way.” Another participant shared her fear of becoming a “prisoner in my own home.” Several web participants provided comments on experiencing suicidal thoughts and social isolation. Another web participant shared that, “at 56 [years old], I don't look sick. I'm surrounded by elderly people who look at me like I'm a liar and faker.”
- **The ability to perform at work.** Participants shared that pain, brain fog, and fatigue have made it difficult or impossible to work effectively. For example, a few participants described the impact of chronic fatigue, sharing “I was too embarrassed to admit I was sleeping on the job.” Participants described giving up on their desired career, being fired, or having to go on disability.
- **Reliance on others.** Participants shared their perspectives on having to rely on caregivers for daily activities. One participant noted, “my wife has begun a daily regimen of pretty much reminding me of what I have to do both for my company and my staff, and myself, and also our daughters.” Another participant, with a heightened sensitivity to hot temperatures, shared, “I have to have my husband, or use a thermometer to check the temperature of baths and showers before I get in.”
- **The significant, often debilitating, impact on relationships.** The majority of participants shared their difficulties in socializing and making plans that were often cancelled due to the severity of their symptoms. Others shared their frustrations that family and friends did not understand the physical and emotional limitations of living with fibromyalgia.

Topic 2: Patient Perspectives on Treatments for Fibromyalgia

The second discussion topic focused on patients’ experiences with therapies used to treat their fibromyalgia. Five panelists provided comments to start the dialogue; all were females living with fibromyalgia, two of whom were also representatives of fibromyalgia-related organizations. Four panelists were middle-aged adults who have lived with fibromyalgia for many years. One panelist developed the condition about five years ago, before the age of 30. Participants described a complex process of trial and error to find an effective multi-modal approach (including drug and non-drug therapies) to fit their specific needs.

In the large-group facilitated discussion that followed, nearly all patients and patient representatives indicated by a show of hands that their experiences (or those of loved ones) were reflected in the panelists’ comments. The facilitated discussion included prescription and over-the-counter drug therapies as well as a variety of non-drug and alternative treatments. Participants’ perspectives on the benefits and downsides of these therapies are summarized below. This section ends with participants’ perspectives on ideal treatments for fibromyalgia, as well as other aspects of fibromyalgia healthcare that they believe are important to consider.

Prescriptions and over-the-counter drugs

According to the polling question (Appendix 3, Q8), nearly all in-person and web participants reported taking or having taken a prescription medication to treat their fibromyalgia symptoms. Prescription drug therapies were described as having widely varying degrees of effectiveness, and many participants

noted limited benefits or decreased benefit over time. Additionally, even if effective, many participants described that they could not sustain treatment because they were unable to tolerate their side effects. Their experiences with specific drugs are summarized below.

Lyrica (pregabalin)

Several participants indicated that Lyrica provides tolerable pain management even if it has not alleviated all of their pain. As one participant explained, “you still have that pain, but you can live with it.” Another shared, “if I miss a dose, I feel it, the neuropathy, the pain, throbbing.” Another participant noted that after starting Lyrica, it was the first time she started “smiling in a long time.”

Some participants commented that they were able to effectively manage the side effects, and others explained that despite difficult side effects, Lyrica has provided sufficient relief to continue treatment. For example, one participant described the use of Wellbutrin (bupropion) in her regimen, to manage excessive sleepiness resulting from Lyrica. Another participant shared that she takes a lower dosage of 100 milligrams/day before bed time, to minimize the impact of cognitive issues and depression that she felt while on Lyrica. Another participant shared that although she had discontinued Lyrica five years prior, she restarted a daily regimen and “It took a while for me to not feel that -- not have the side effects. I pushed past it. I pushed through it. And I don’t have any side effects at all from it.”

However, many other participants commented on the intolerable downsides of Lyrica. Several commented on discontinuing Lyrica after a few weeks because of the negative effects, most notably drowsiness, cognitive issues, dizziness, effects on mood, and weight gain. Other side effects noted by in-person and web participants included depression, and swelling of the mouth and tongue. One participant shared, “I can’t take Lyrica because it severely affects my vision and handwriting.” Others shared that Lyrica lost effectiveness after some time. One web participant shared, “Lyrica only worked for me for about 2 years, and then it stopped working. I gained 40 pounds while on Lyrica.” A few participants specifically mentioned withdrawal symptoms after discontinuing Lyrica.

Cymbalta (duloxetine)

Many participants noted they take or have taken Cymbalta as part of their overall treatment regimen. One participant noted, “I am on Cymbalta, and that helps -- that gives me energy. And it helps with my overall body pain.” Similar to Lyrica, several participants noted that despite negative side effects (such as headaches and vertigo), they continued Cymbalta to manage their fibromyalgia symptoms. For example, one participant mentioned that she took Cymbalta despite “eight to 12 bowel movements a day. It also cut the appetite. I have lost considerable weight.”

Many participants shared significant side effects to Cymbalta. One web participant noted, “I stopped taking Cymbalta after taking it for nearly five years about two months ago. The Cymbalta really helped with the pain, but the side effects, which are exacerbated by taking Imitrex (sumatriptan) and tramadol, became too much.” Another shared “Cymbalta causes significant cognitive issues for me, literally bringing me to a point where I couldn't complete a sentence. It was so unexpected I didn't even know to look for it.” Participants also shared experiences of weight gain, swelling of the mouth and tongue, vision problems, and suicidal thoughts.

Savella (milnacipran)

A few participants shared positive experiences taking Savella to treat their fibromyalgia symptoms. One web participant noted that Savella successfully helped to reduce the severity and frequency of flare ups. Another participant, weighing the drug's benefits against its side-effects, said, "Savella absolutely was wonderful for the pain," but that even on low doses, she experienced "a year of continual morning sickness" and eventually had to discontinue the medication. Other participants also shared side effects that they experienced while on Savella. One participant commented, "I have tried Savella. I ended up in the hospital because my blood pressure was so high and I was vomiting and I couldn't keep any food down. I just felt horrible." Many in-person and web participants shared that they had also tried Savella, but that it was ineffective or had side effects that were intolerable.

Opioids

Opioids, and in particular hydrocodone, were the most frequently mentioned prescription pain relievers. Participants reported a wide range of experiences and perspectives on opioids. Most participants noted that opioids are effective and significantly increased their quality of life when compared to other available treatments. Some shared that they take a low-dose opioid for pain management on a daily basis. The following examples illustrate the positive experiences shared by in-person and web participants in the discussion of opioids.

- "[Hydrocodone] allows me to live my life without fear of the pain because I have a tool to manage it."
- "I am completely symptom free for the middle hours between my hydrocodone doses."
- "The best medications I have taken [are], in fact, opioids. No side effects. And for the last three and a half years I have had the best quality of life that I have had since I was a teenager."

Participants who report using opioids described their challenges in accessing these treatments and the stigma they face. These challenges included being "treated like a drug addict," having to "travel quite a ways to get a doctor who will prescribe the medication," and a lack of understanding by insurance companies.

Some participants however, commented that they were unable or unwilling to take opioids due to a range of side effects, including feeling high, mental excitability, sleep issues, itching, and concern about abuse.

Other prescription therapies

- Participants mentioned using antidepressants, including amitriptyline, Zoloft (sertraline), Effexor (venlafaxine), and Abilify (aripiprazole), to address symptoms, particularly depression and sleep issues. One participant noted the importance of managing her depression symptoms, commenting "With my...depression in remission, I am much more emotionally able to deal with the remaining pain symptoms." Trazodone was frequently mentioned as a drug used for sleep. One patient noted the use of a "custom mix of Remeron (mirtazapine) for deep sleep."

- Participants shared that they have experienced pain relief through other routes of administration, including Imitrex injections (for migraine headaches) and routine epidurals. One participant commented that she periodically undergoes nerve ablation therapy, but that “the treatments can be very painful in and of themselves and cause flares.” Another participant commented that periodic Botox injections feel like a “bee sting with every pick of the needle...but it works.” A range of pain patches including lidocaine patches and gels, including Voltaren (Diclofenac), were mentioned for targeted pain relief.
- Participants also described using stimulants to treat fatigue, again with varying degrees of effectiveness. One webcast participant noted that stimulants were “extremely effective” in providing energy, whereas another shared that she had “no success with stimulants, it causes insomnia that lasts for days and then a flare up lasting for weeks.”
- A variety of other drugs were mentioned, including muscle relaxants, antihistamines, sleep aids, and a few over-the-counter non-steroidal anti-inflammatory drugs.

Non-drug therapies

Participants emphasized the importance of a holistic approach to managing fibromyalgia symptoms. A summary of these therapies is listed below.

- Several non-drug or physical therapies were mentioned, including trigger point injections, Transcutaneous Electrical Nerve Stimulation (TENS) unit therapy, acupuncture, massage, heat and ice therapy, and dry needling (for myofascial pain). Overall, participants noted some level of relief from these treatments.
- Some participants commented on relaxation, emotional or psychosocial therapies, including yoga, meditation, guided imagery, breathing exercises, and biofeedback training. Other participants commented that emotional and social support and reducing stress were critical to their ability to manage symptoms.
- Several participants shared that pacing was an important part of their therapy. One participant noted, “I also learned how to pace myself. But when I don’t do it, that’s when I have that brain fog, and that’s when I fall or bump into things.” Another participant specifically noted that it was important “to be mindful of my posture and stress levels....if I overdo my physical activities...some pain does return.” Another participant relied on bodily cues, sharing, “I know that pain in one of my shoulders means that I need to stop what I’m doing and rest immediately.”
- A wide variety of vitamins, herbs, and dietary supplements were mentioned as being used to treat specific symptoms, including rhubarb for constipation, lavender, St. John's wort oil, aloe vera for neck pain, Myer’s cocktail for fatigue, melatonin for sleep issues, and vitamin D.
- Several participants mentioned that medical marijuana was effective in treating their pain, sleep issues, nausea, and anxiety.

- Participants mentioned the importance of diet modifications and exercise to manage their fibromyalgia symptoms. This included avoiding fried foods, dairy products, and gluten. One participant noted that she became an organic vegetarian which helped to alleviate the side effects of her fibromyalgia treatments. Several participants noted that they incorporate exercise into their lifestyle, such as swimming, Pilates, using an elliptical machine, or light biking whenever they were able to.

Treatment downsides

- Many participants described the significant impact of treatment side effects, especially when taken over the long-term. One participant noted that “the longer that I’m on the medications the more side effects I seem to start developing.”
- Some participants commented that their therapies had initial success, but became less effective with time. One participant noted that after four years of effectiveness, “my trigger point injections stopped working.” Another shared, “I was on Ultram for four or five years or longer. It had stopped working completely, but I was still taking it, trying to give it a chance.”
- Some participants expressed concerns on the long-term toxicity of drugs and how side effects may change due to prolonged use. One younger participant noted her fears of becoming pregnant after years of using high-dose medications.
- A few participants commented on the cost of treatment, including out-of-pocket costs for treatments not covered by insurance. One participant noted, “We spend \$25,000 a year out-of-pocket on medical treatments.”

Perspectives on an ideal treatment for fibromyalgia

Participants provided feedback on what they would look for in an ideal treatment for fibromyalgia. Many participants stressed that ideal treatment begins with the medical community’s increased understanding of fibromyalgia and its symptoms. Participants commented that diagnostic processes should be improved so that a customized treatment plan can be established based on a correct diagnosis.

Participants also shared that an ideal treatment would have fewer side effects and address the pervasive symptoms of fibromyalgia. One participant summarized, “An ideal treatment would address the all-over pain, insomnia, and fatigue while also allowing clear-headed thinking and memory without fatigue or weight gain.” Another participant commented that “due to stomach problems... [ideal treatment would be] chewable, dissolvable, or in liquid form.”

Throughout the meeting, participants raised a number of other considerations that they believed were important relating to fibromyalgia drug development or treatment more broadly. Participants expressed concern that fibromyalgia may be underdiagnosed or misdiagnosed. They described their own difficulty in receiving a diagnosis, particularly if they also have co-morbid conditions. They also commented on the need to understand how patients experience fibromyalgia symptoms and treatment side effects when they have comorbid conditions.

Additionally, several issues were raised that participants strongly felt required further research and education. For example, several in-person and web participants wanted to better understand the link between fibromyalgia (and treatment options) and fertility problems, and if there was a relationship between fibromyalgia and menopause. Others stressed the importance of determining whether there is a hereditary component to fibromyalgia.

Summary of Comments Submitted to the Public Docket

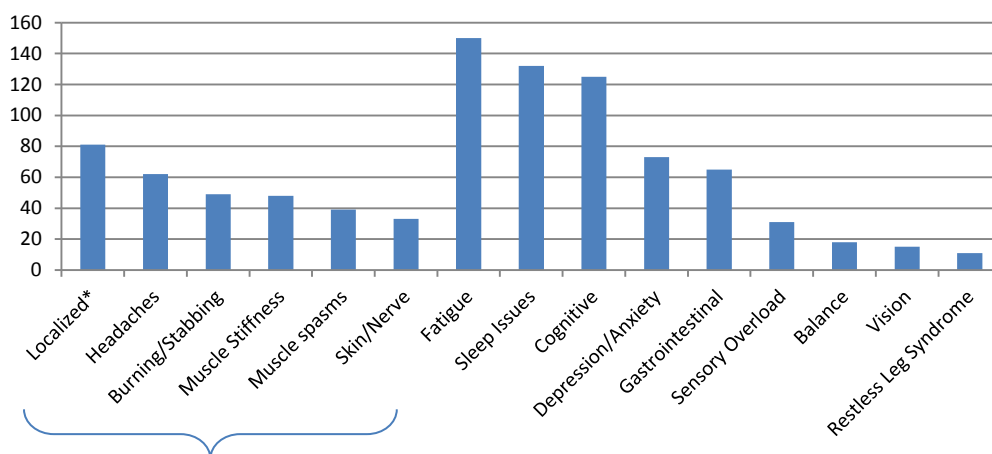
FDA received approximately 400 comment submissions to the public docket that supplemented the Patient-Focused Drug Development meeting on fibromyalgia. The majority of comments were submitted by patients, with a few comments from patient caregivers. FDA also received comments from three advocacy groups, National Fibromyalgia Partnership (NFP), National Fibromyalgia & Chronic Pain Association (NFMCPA) and PatientsLikeMe (PLM) Fibromyalgia Community. Each organization gathered perspectives of fibromyalgia patients and submitted the results to the public docket.

Overall, the comments received in the docket reflected the experiences and perspectives shared at the March 2014 meeting. They further elaborated on several issues raised during the meeting. The following is a summary of comments provided on fibromyalgia symptoms, impacts, and current treatments. Particular focus is placed on experiences or perspectives that were not raised or addressed in detail at the meeting.

Submitted comments on symptoms of fibromyalgia

Nearly 30 different types of symptoms were identified by docket commenters. The table below shows the counts of the most frequently-mentioned symptoms. Observations gathered from the NFP, NFMCPA, and PLM reports showed similar findings in the range of symptoms that are experienced.

Table 1: Count of Docket Comments that Describe Specific Fibromyalgia Symptoms



Descriptions of Pain Manifestation, categorized in six unique ways.
Localized* - Includes joints & tender points

- There were 270 docket comments that described **chronic pain** in some detail. Commenters reiterated that they experience pain in varying degrees, from persistent muscle fatigue to periods of burning, shooting pain. One docket commenter noted, “my body is constantly pinging and ticking and aching,” while another shared, “my feet burn and I feel like I’m being bitten by thousands of fire ants.” Chronic pain was generally described as widespread pain and/or localized to specific joints or muscles.
- **Headaches** were also among the most commonly mentioned symptoms in the docket. Commenters shared persistent migraines that, as one commenter shared, “leave [his wife] unable to do much more than lie in a dark room with ice packs.” Commenters described debilitating “headaches that hurt so bad that I can’t stand to move or speak.”
- Many commenters emphasized the burden of **chronic fatigue**. This was described by most as a combination of being easily fatigued by physical activity and feeling exhausted at all times. One commenter shared her experience with chronic fatigue by noting, “It seems no matter how long I sleep, when I sleep, or how deeply I can sleep, I am always tired.”
- The majority of commenters also noted a range of **sleep problems**, including insomnia, unrefreshing sleep, and disrupted sleep. Many commented on the burden of not being able to achieve restorative sleep. One participant shared that “every day is a struggle to get out of bed because I haven’t slept through the night.”
- Most docket commenters also shared that **cognitive issues**, including memory loss and brain fog, were a common symptom of fibromyalgia. Some shared that brain fog was worsened by the chronic fatigue and pain. Commenters described the inability to form words, difficulties in multi-tasking, confusion, and recalling and remembering information.
- Many commenters noted that persistent pain and fatigue led to severe **depression** and a feeling of hopelessness. As one commenter shared, “My life is like a kaleidoscope of symptoms but I am not in control of turning the viewer to see what’s going to happen to me next, and I never know when they will hit.” Others shared the struggle of appearing to look “normal” on the outside but living with severe fibromyalgia symptoms that were at many times not understood by others.

Submitted comments on the overall impact of fibromyalgia on daily life

The docket comments reflected the input received during the meeting on the debilitating impact that fibromyalgia has on patients’ daily lives, and the significant social, emotional, and financial toll the disease has on patients and their families.

- Most commenters reiterated the impacts on **personal and family life**, including difficulties taking care of themselves and their children and managing their household. Many described how simple physical activity, such as playing with their children or vacuuming their home led to severe pain and exhaustion. Docket commenters focused more attention on being dependent on others for basic care, particularly in severe cases. Caregivers provided a unique and important perspective; one caregiver shared that when symptoms are severe, he is on duty “24/7” to care for his wife. Another caregiver shared her fear on the worsening of symptoms for her loved one.

- Many commenters also emphasized the impacts on **job performance**, from not being able to work at all to limitations on how much they can work. As one commenter summarized, “fibromyalgia has stopped me in my tracks and stolen my career from me.” Others shared the impact of specific symptoms on their professional life, explaining, “I had to quit working because I had brain fog that disrupted the focus I needed,” and “I could work for no longer than two hours at a stretch without having to lay down to rest.”
- Many commented on the **social impacts** of fibromyalgia symptoms, such as on their ability to plan social engagements and being able to reliably spend time with others. Commenters shared that plans are often cancelled last minute because of symptoms, which has led many to strained relationships. Others noted they feel isolated and depressed from not being able to participate in activities. As one commenter summarized, “I have seen my life go from energetic and fun-filled to painful and exhausting.”
- Several commenters also reiterated concerns and frustration regarding the **lack of understanding in the medical community**. Many shared experiences of the difficulties in finding doctors who understood their condition, being prescribed helpful medications, and being taken seriously about their condition. As one commenter summarized, “I feel very discouraged by the way I'm treated by doctors and the general public. There is not enough awareness, and much too much disbelief aimed at those of us suffering from this terrible illness.” Finally, many commenters shared their fear on worsening symptoms and hoped for a cure for fibromyalgia.

Submitted comments on current treatments for fibromyalgia

The submitted comments reflected the challenges of managing the many symptoms of fibromyalgia, while making difficult decisions about treatments. The range of commenters’ experiences was similar to those at the public meeting. The prescription drug therapies mentioned most frequently were Lyrica, Cymbalta, Savella, and opioid treatments. Non-drug therapies were also frequently mentioned, including diet modifications and exercise regimens, vitamins and supplements, physical therapy and chiropractic treatments, and massage. Commenters’ experiences with prescription and non-drug therapies emphasized the variability of benefits and side effects for different patients. More detail is provided below.

- **Lyrica (pregabalin):** Nearly 100 docket commenters described past and present experiences with Lyrica, reiterating the meeting input on the variability in patients’ experiences. A few commenters reported that the benefits of Lyrica currently outweigh the downsides. As one said, “While the Lyrica does not take all of the pain away, I can definitely tell a difference when I may forget to take it, the pain reminds me.” Another shared, “I stick with Lyrica even though I still have nausea.” However, others reported little to no benefit and were troubled by the side effects, including weight gain, dizziness, sleep issues, fatigue, and mood disruptions.
- **Cymbalta (duloxetine):** Over 100 docket commenters described experiences with Cymbalta. Several shared that they felt relief from their symptoms after taking Cymbalta, with one commenting, “It has been a miracle drug for me! I don't know what I would have done if I hadn't found this drug.” Some shared that the side effects of Cymbalta made it difficult to continue. As one commenter reported, “I loved having no pain with the Cymbalta, but I need my brain to work.” Others shared additional side effects, similar to those reported during the meeting, including sleep issues, fatigue, mood disruptions, headaches, loss of libido, dry mouth, and

nausea. Many shared their experiences with discontinuing Cymbalta due to its side effects, only to experience severe withdrawal symptoms.

- **Savella (milnacipran):** Over 40 docket comments were provided on experiences with Savella. Most comments were similar to what was heard during the public meeting and focused on the side effects of Savella, including high blood pressure, nausea, excessive sweating, and mood swings. Several commenters noted that Savella did not provide any relief for their symptoms.
- **Neurontin (gabapentin):** Nearly 60 comments were submitted on experiences with Neurontin, or generic gabapentin. Comments generally noted that gabapentin provided some relief for pain, with one person commenting, “it helps immensely with most pain, but not all.” Others commented that gabapentin did not provide any relief, or that the side effects, including drowsiness, swelling, and pain, were not tolerable enough to continue therapy.
- **Opioids/Narcotics:** Similar to the public meeting, the majority of submitted comments were related to the use of opioids and narcotics to manage fibromyalgia symptoms. Many reported significant benefits from these therapies, noting that opioids provided them with the ability to function during the day. Many shared their experiences with trying a range of other prescription drugs before taking opioids. They acknowledged the potential for misuse of opioids but reiterated the benefits that they experienced when taking these therapies responsibly. As one commenter concluded, “Please do not take away our opioid pain medication.”
- **Other drug therapies:** A range of other drug therapies were mentioned, including muscle relaxants, pain patches and gels, trigger point injections, and sleep medications.
- Discussion on **non-drug therapies** closely resembled input received during the meeting. The majority of docket comments stressed the benefits of diet modifications and light exercise in managing fibromyalgia symptoms. Massage, acupuncture, and vitamin and herbal supplements were also frequently mentioned.

Submitted comments on ideal treatments for fibromyalgia

Several perspectives were provided on ideal treatments for fibromyalgia. The top three aspects of ideal treatments that commenters provided were on the treatment of chronic pain, treatment of chronic fatigue, and treatments with minimal to no side effects. Other aspects of ideal treatments included affordability, minimal health impacts when used over the long-term, holistic treatment approaches, and increased knowledge in the medical community on fibromyalgia.

Conclusion

This meeting was the sixth of the Patient-Focused Drug Development meetings. It allowed FDA to obtain patients’ in-depth point of view on the severity of fibromyalgia, its impact on daily life, and available treatment options. FDA recognizes that patients have a very unique ability to contribute to our understanding of the broader context of this disease, which is important to our role, and that of others, in the drug development process. We are grateful to all of the participants who so thoughtfully and courageously shared such personal stories and perspectives.

It is clear that fibromyalgia 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. We truly admire the spirit of the participants, who demonstrated their fortitude in the face of adversity presented by their fibromyalgia. We share the patient community's desire and commitment to furthering the development of safe and effective drug therapies.

Appendix 1: Meeting Agenda and Discussion Questions



Fibromyalgia Public Meeting on Patient-Focused Drug Development



March 26, 2014

12:00 – 1:00 pm	Registration
1:00 – 1:05 pm	Welcome Sara Eggers, PhD <i>Office of Strategic Programs (OSP), Center for Drug Evaluation and Research (CDER), FDA</i>
1:05 – 1:10 pm	Opening Remarks Bob Rappaport, MD <i>Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), CDER, FDA</i>
1:10 – 1:20 pm	Overview of FDA’s Patient-Focused Drug Development Initiative Patrick Frey, MPP <i>Director, Office of Program and Strategic Analysis, CDER, FDA</i>
1:20 – 1:30 pm	Background on Fibromyalgia and Therapeutic Options Elizabeth Kilgore, MD <i>Medical Officer, DAAAP, CDER, FDA</i>
1:30 – 1:40 pm	Overview of Discussion Format Sara Eggers, PhD <i>OSP, CDER, FDA</i>
1:40 – 2:10 pm	Panel #1 Comments on Topic 1 Topic 1: Disease symptoms and daily impacts that matter most to patients. A panel of patients and patient representatives will provide comments to start the discussion.
2:10 – 3:00 pm	Large-Group Facilitated Discussion on Topic 1 Patients and patient representatives in the audience are invited to add to the dialogue.
3:00 – 3:15 pm	Break
3:15 – 3:45 pm	Panel #2 Comments on Topic 2 Topic 2: Patients’ perspectives on current approaches to treating fibromyalgia.
3:45 – 4:25 pm	Large-Group Facilitated Discussion on Topic 2
4:25 – 4:55 pm	Open Public Comment

Sharon Hertz, MD

Deputy Director, DAAAP, CDER, FDA

Discussion Questions

Topic 1: Disease symptoms and daily impacts that matter most to patients

- 1) Of all the symptoms that you experience because of your condition, which 1-3 symptoms have the most significant impact on your life? (Examples may include chronic pain, fatigue, difficulty concentrating, sleep disorders, etc.)
- 2) Are there specific activities that are important to you but that you cannot do at all or as fully as you would like because of your condition? (Examples of activities may include sleeping through the night, daily hygiene, driving, household chores, etc.)
 - a) How do your symptoms and their negative impacts affect your daily life on the best days? On the worst days?
- 3) How have your condition and its symptoms changed over time?
 - a) Do your symptoms come and go? If so, do you know of anything that makes your symptoms better? Worse?
- 4) What worries you most about your condition?

Topic 2: Patients' perspectives on current approaches to treating fibromyalgia

- 1) What are you currently doing to help treat your condition or its symptoms? (Examples may include prescription medicines, over-the-counter products, and other therapies including non-drug therapies such as exercise.)
 - 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) How well do these treatments improve your ability to do specific activities that are important to you in your daily life?
 - b) How well have these treatments worked for you as your condition has changed over time?
- 3) What are the most significant downsides to your current treatments, and how do they affect your daily life? (Examples of downsides may include bothersome side effects, going to the hospital for treatment, restrictions on driving, etc.)
- 4) What specific things would you look for in an ideal treatment for your condition?

Appendix 2: FDA and Patient Panel Participants

FDA Panelists

Bob Rappaport	Anesthesia, Analgesia, and Addiction Products (DAAAP), CDER
Sharon Hertz	DAAAP, CDER
Ellen Fields	CDER
Elizabeth Kilgore	DAAAP, CDER
Patrick Frey	Office of Strategic Programs, CDER

Patient Panelists

Topic 1

Sabrina Dudley-Johnson - Patient

Laura Dugan - Patient

Michele Dunckel - Patient

Lori Galpeer - Patient

Jacob Smith - Patient

Topic 2

Jan Chambers – Patient

Gwenn Herman - Patient

Sarah Lyall - Patient

Nancy Ryan - Patient

Deborah Ward - Patient

Appendix 3: Meeting Polling Questions

1. Where do you live?
 - a. Within Washington, D.C. metropolitan area (including the Virginia and Maryland suburbs)
 - b. Outside of the Washington, D.C. metropolitan area
2. Do you have fibromyalgia?
 - a. Yes
 - b. No

We asked that the remainder of the questions be answered by people who responded “yes” to Question 2.

3. What is your age?
 - a. Younger than 30
 - b. 31 – 40
 - c. 41 – 50
 - d. 51 – 60
 - e. 61 – 70
 - f. 71 or greater
4. Are you:
 - a. Male
 - b. Female
5. How long have you had symptoms of fibromyalgia?
 - a. Less than 5 years
 - b. 5 – 10 years
 - c. 10 – 20 years
 - d. More than 20 years
 - e. I’m not sure
6. Do you have a physician-confirmed diagnosis of fibromyalgia?
 - a. Yes
 - b. No
 - c. I’m not sure

Question for Topic 1

7. Of all the symptoms that you experience because of your condition, which do you consider to have the most significant impact on your daily life? Please choose up to 3 symptoms.
 - a. Chronic pain
 - b. Fatigue or lack of energy
 - c. Difficulty concentrating or memory problems
 - d. Sleep problems

- e. Sensitivity to light, sound or other stimuli
- f. Gastrointestinal issues
- g. Depression or anxiety
- h. Other symptoms not listed above

Question for Topic 2

8. What are you currently doing to treat your condition or its symptoms? Check all that apply.
- a. Prescription medicines
 - b. Over-the-counter products
 - c. Exercise
 - d. Physical therapy, massage, or acupuncture
 - e. Dietary supplements or diet changes
 - f. Lifestyle changes, such as pacing activities or avoiding stressful situations
 - g. Behavioral therapies such as pain programs or support groups
 - h. Other therapies
 - i. I'm not sure
 - j. I am not doing or taking any therapies

Appendix 4: Incorporating Patient Input into a Benefit-Risk Assessment Framework for Fibromyalgia

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.³ 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 Fibromyalgia 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 Fibromyalgia below draws from various sources, including what was discussed at the Fibromyalgia Patient-Focused Drug Development meeting held on March 26, 2014. This sample framework contains the kind of information that we anticipate could be included in a framework completed for a drug under review for Fibromyalgia. 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.

³ 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>.

Sample Fibromyalgia Benefit-Risk Assessment Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> – Fibromyalgia is a chronic condition characterized by wide-spread pain in the body’s soft tissues that lasts more than 3 months. – It is estimated that Fibromyalgia afflicts five million adults in the United States. Although the disorder can affect both men and women of all ethnicities, women make up about 80-90 percent of those diagnosed. – Most patients are diagnosed during middle age. Prevalence increases with age, and many report that symptoms worsen over time. – Pain symptoms are experienced in various localized points, as well as in the muscles, nerves, and skin. Other symptoms experienced include chronic fatigue, sleep dysfunction, cognitive impairment, headaches, gastrointestinal issues, and oversensitivity to stimuli. – Symptoms can have considerable detrimental effects on a patient’s quality of life, ability to function in daily activities, and overall social and societal engagement. Patients report living with constant stigmatization, anxiety, depression, and fear of ongoing or worsening symptoms. – <i>Refer to the Voice of the Patient report for a more detailed narrative.</i> 	<p>Fibromyalgia is a chronic, debilitating disorder that is most commonly diagnosed among women. The disease can have a debilitating effect on patients’ day-to-day functioning and take a significant physical, emotional, and social toll on patients’ quality of life.</p>
Current Treatment Options	<p>There are three FDA-approved drug treatments for fibromyalgia including:</p> <ul style="list-style-type: none"> ○ Lyrica (pregabalin): Indicated to treat nerve and muscle pain associated with fibromyalgia. The most frequently occurring adverse reactions include dizziness, somnolence, dry mouth, edema, blurred vision, weight gain and thinking abnormal (primarily difficulty with concentration/attention). ○ Cymbalta (duloxetine): Antidepressant approved for pain relief in fibromyalgia patients. The most frequently occurring adverse reactions include nausea, dry mouth, somnolence, fatigue, constipation, decreased appetite, and hyperhidrosis. ○ Savella (milnacipran): Antidepressant approved to treat fibromyalgia symptoms such as pain, fatigue, and cognitive difficulties. The most frequently occurring adverse reactions include nausea, headache, constipation, dizziness, insomnia, hot flush, hyperhidrosis, vomiting, palpitations, heart rate increased, dry mouth, and hypertension. <ul style="list-style-type: none"> – Patients use a number of other drugs including opioid and narcotic pain relievers, anti-convulsants, anti-depressants, muscle relaxants, NSAIDs, trigger point injections, and topical pain relievers. – Non-drug therapies most commonly mentioned by patients include massage, physical therapy, acupuncture, and vitamin supplements. – Most patients included diet modifications, light exercise, and other lifestyle changes as part of their symptom management. – <i>Refer to the Voice of the Patient report for a more detailed narrative.</i> 	<p>Drug treatments are available for the symptoms of fibromyalgia; however, efficacy varies from patient to patient, and significant side effects can limit benefits or preclude use of these medications. Thus, there is a continued need for additional effective and tolerable treatment options for patients to improve their daily functioning.</p>