

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

Narcolepsy

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Table of Contents

Introduction	3
Overview of narcolepsy	3
Meeting overview	3
Report overview and key themes	4
Discussion Topic 1: Disease Symptoms and Daily Impacts That Matter Most to Patients.....	6
Perspectives on most significant symptoms.....	6
<i>Experiences with symptoms changing over time</i>	9
Perspectives on the overall impact of narcolepsy on daily life.....	10
Discussion Topic 2: Patient Perspectives on Treating Narcolepsy	11
Experiences with prescription drug therapy.....	11
Perspectives on non-drug therapies	13
Perspectives on ideal treatment for narcolepsy.....	14
Other considerations on treating narcolepsy	15
Summary of Comments Submitted to the Public Docket	15
Submitted comments on symptoms of narcolepsy.....	15
Submitted comments on the overall impact of narcolepsy on daily life	16
Submitted comments on current treatments for narcolepsy.....	17
Conclusion.....	18
Appendix 1: Meeting Agenda and Discussion Questions.....	19
Appendix 2: Patient and FDA Panel Participants.....	21
Appendix 3: Meeting Polling Questions.....	22
Appendix 4: Incorporating Patient Input into a Benefit-Risk Assessment Framework for Narcolepsy	24

Introduction

On September 24, 2013, FDA held a public meeting to hear perspectives from people living with narcolepsy 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 the next five years, each focused on a specific disease area.

Overview of narcolepsy

Narcolepsy is a rare and under-diagnosed chronic condition that is estimated to affect more than 1 in 2,000 Americans. The condition is characterized by several symptoms, including excessive daytime sleepiness (EDS), cataplexy, automatic behaviors (performing actions such as walking, eating, or driving, in a semiconscious way without awareness), hallucinations, and sleep paralysis. Symptoms vary from patient to patient and generally first appear between the ages of 7 and 25. Many people with narcolepsy experience cataplexy, a condition that causes a sudden reduction or loss of muscle tone while a patient is awake. This muscle weakness, which may last seconds or minutes, can cause slurred speech and can affect specific body parts or the entire body. Narcolepsy patients often experience difficulty sleeping at night. Most patients have difficulty functioning at school, work, and home, as well as in social situations.

Narcolepsy has no cure, but drug therapies and lifestyle changes can often help improve symptoms and quality of life. There are five drug treatments approved to treat patients with narcolepsy: Xyrem (sodium oxybate), Provigil (modafinil), Nuvigil (amodafonil), methylphenidate, and amphetamine. There are no FDA-approved drugs specifically for pediatric use in treating narcolepsy. Other prescription drugs are also used off-label for narcolepsy, including stimulants, depressants, and antidepressants. Lifestyle modifications, such as regular napping, control over diet, and exercise, can also help improve or manage disease symptoms or treatment side effects.

Meeting overview

This meeting provided FDA the opportunity to hear directly from patients, patient caretakers, and patient advocates about their experiences with narcolepsy and its treatments. 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 narcolepsy. 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. 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 able to submit comments throughout the discussion, and their comments have been incorporated into this summary. 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 70 narcolepsy patients or patient representatives attended the meeting in-person, and over 50 patient or patient representatives provided input through the live webcast and polling

questions. The participation rate was considered high for a meeting on a rare disease. According to their responses to the polling questions, in-person and web participants represented a range of patients, with a higher proportion of women, adults aged 20 to 50, and patients diagnosed in the past 10 years. Although participants at this meeting may not fully represent the population living with narcolepsy, we believe that the input received reflects a range of experiences with narcolepsy 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](#),¹ which was open until November 25, 2013. 175 comments were submitted to the public docket, the majority by individual narcolepsy patients or their caregivers. One submitted comment contained data from a survey of narcolepsy patients and patient representatives conducted by a consortium of patient advocates, Unite Narcolepsy. An interim analysis of this survey was discussed at the September 24 meeting.²

More information, including the archived webcast recording and meeting transcript, is available on the meeting website: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm359018.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 docket, beginning on page 15. To the extent possible, the terms used in this summary to describe specific narcolepsy symptoms, impacts and treatment experiences reflect the words used by in-person or web participants or docket commenters. The report reflects the content of this meeting and is not meant to be representative in any way of the views and perceptions of the entire narcolepsy patient population or any specific group of individuals or entities. There may be symptoms, impacts, or treatment experiences not mentioned in the report.

The input from the meeting and docket comments underscore the chronic and debilitating effect that narcolepsy 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:

- Excessive Daytime Sleepiness (EDS), a hallmark of this disease, was identified by most participants as the most significant symptom affecting their daily lives. They stressed that the effects of EDS go far beyond feeling tired or falling asleep during the day. Because of EDS, they constantly battle “brain fog” and other cognitive impairments, automatic behaviors, and chronic sleeping deprivation.
- Narcolepsy, however, is much more than EDS. For those who experience cataplexy, hallucinations or sleep paralysis, the uncontrollable and often unpredictable loss of control can be terrifying. For some patients, other related symptoms, such as insomnia, weight gain, mood fluctuations, and depression, have a significant impact on their lives.

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.

² More information can be found at www.unitenarcolepsy.org/.

- Narcolepsy patients' symptoms often change over time. Participants identified an apparent cyclical (e.g., seasonal, monthly) nature of their symptoms, particularly with respect to their ability to sleep. For some, their symptoms, even when treated, have gotten consistently worse over time. Others have developed new symptoms (such as cataplexy) over time.
- Narcolepsy is a debilitating condition that can exert a significant social, emotional, and financial toll on patients and their families. Participants described their difficulty in maintaining a job or attending school, caring for their households, engaging in social situations, and maintaining relationships. For some, the stigma of being labelled lazy, careless, or incapable by colleagues, health care professionals, and others is very frustrating.
- Almost all participants use prescription medications to treat their condition, and for many, these drugs have drastically improved their symptoms. The side effects of these drugs, however, have a significant impact on many patients' lives, and some have had to give up a beneficial drug because of intolerable side effects or development of tolerance. Non-drug therapies, such as scheduled naps, diet modification, and exercise, play an important role in helping narcolepsy patients manage their condition. These mechanisms, however, can be challenging to sustain.
- Patients see a continued need to enhance the treatment armamentarium, given current challenges with variability in effectiveness, tolerability, and access to currently-available treatments. Patients "don't want narcolepsy to control" them. They want to control their narcolepsy.
- Participants stressed the importance of recognizing the broader challenges people with narcolepsy face in: (a) getting proper diagnosis and treatment, and (b) getting the support they need in their schools, workplaces, and communities.

The patient input generated through this meeting and the docket comments strengthens FDA understanding of the burden that narcolepsy has on patients, as well as the various ways that patients try to manage their symptoms and the side effects they experience. FDA staff will carefully consider this input when advising sponsors on their drug development programs and when assessing products under review for marketing approval. For example, *Appendix 4* shows how this input may support our benefit-risk assessments for products under review. This input may also be useful to the drug development process more broadly, for example, by identifying potential areas of unmet need for narcolepsy patients or opportunities for development of new outcome measures in clinical trials, e.g., relating to cognitive effects.

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

The first discussion topic focused on patients' experiences with their narcolepsy symptoms and the resulting impacts those symptoms have on patients' 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 to because of their condition.

A panel of five narcolepsy patients provided initial comments to start the dialogue. The panel included two young adults who were recently diagnosed and three older adults who suffered with symptoms for many years prior to being diagnosed. These participants' testimonies offered a broad look at the symptoms and impacts of narcolepsy, and provided a rich context for the subsequent dialogue. The panel participants described specific challenges with excessive daytime sleepiness, cataplexy, sleep dysfunction, hallucinations, confusion, difficulty concentrating, mood fluctuations, and obesity. They offered concrete examples of the impact that their symptoms have on their ability to get out of the house in the morning, perform in work or school, take care of their families, maintain relationships, and ensure their safety. They also described the significant frustration, stress, and shame that they have experienced because of their condition.

In the large-group facilitated discussion that followed the panel comments, 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. According to a polling question (Appendix 3, Q6), "excessive daytime sleepiness" was identified as a "top 3" significant symptom by nearly all responding participants, followed by "difficulty sleeping", "cataplexy", "hallucinations while waking up or falling asleep" and "other" symptoms (each reported by approximately one-third of responding participants). Responding web participants reported similar results.

Perspectives on most significant symptoms

The range of symptoms discussed by in-person and web participants is described in more detail below.

Excessive daytime sleepiness

The most frequently discussed symptom by in-person and web participants was **excessive daytime sleepiness (EDS)**. Participants described EDS as a persistent, encompassing state of extreme drowsiness and an overwhelming fatigue that "most people just don't understand." As one participant explained, "[I fight] a constant battle between being asleep and being awake, never really sure which realm I'm actually in."

Participants described several ways that EDS manifests, to varying degrees. One effect described in much detail was "sleep attack," or having little or no control over falling asleep. As one participant commented "[t]he desire to sleep [is so powerful] that nothing else matters." Participants described falling asleep during class or while performing "mundane tasks" such as working on the computer, eating, speaking or driving. A few said that they fall asleep after even the briefest period of physical inactivity, for example, "if [someone] talks to me for more than one minute without requiring a response." Several web participants described "mini" or "microsleeps" that last for only a few seconds and which may be mistaken, for example, as merely "staring off for a period of time."

The EDS effects that received the most attention, however, were the **chronic cognitive effects**, or as participants termed them, a pervasive “brain fog” or “half-sleep state.” Specific effects (using participants’ terms) included being in a daze, forgetfulness, lack of alertness and focus, difficulty thinking, blurred vision, losing brain organization, and extreme confusion. Web participants also identified difficulty word finding, decrease in mental agility, and feeling “like you’re drunk.” The following is a sample of experiences shared:

- One participant described going from one extreme, “talking a lot and not making sense,” to another extreme, “a blank stare.” She stated that these effects were unpredictable and could happen “four times a day at the least, and it would last either 10 minutes or a couple hours.”
- One participant described effects on concentration: “There were times that I was very much on target... and then other times it would take me a very long time to generate the simplest of work because I just wasn’t focused.”
- One participant described brain fog as feeling “as if I’m floating on a cloud through life... a gray and rainy one. My head always feels heavy, my vision is usually blurred, and I never feel clear.”

In addition to the cognitive effects, many in-person and web participants described **automatic behaviors** that occur without awareness while being asleep or in the “half-sleep state.” The following examples illustrate their experiences:

- Many participants described engaging in conversation without awareness: “Imagine waking up and looking at your phone and realizing you had several lengthy conversations with no memory of them.” Another participant described his wife’s experience as a kind of “conscious sedation. She can be completely with a conversation and completely be out of it at the same time.”
- Some participants described conducting routine work activities, including one participant who described being unaware of this behavior until a co-worker later complained: “I was trying to hold a conversation with you, and you just continued to type and design.”
- A few participants described random or nonsensical actions, such as putting “the remote control to the TV in the box of fish sticks, and it makes total sense when you’re doing it.”
- A few participants described having placed themselves in dangerous situations, such as crossing a busy highway, without awareness or recollection. One participant described how, before having her condition under control, she would “nod off into a deep daze” while driving and “lose entire chunks of 20, 30 minutes of time.”

FDA asked participants whether participants experienced these automatic behaviors always at a time of sleepiness, or if they ever experienced them when not sleepy. Several participants, particularly web participants, indicated that these events are often unpredictable and can happen with or without preceding sleepiness. As one web participant commented, “sometimes you can feel it coming. Other times, it’s out of the blue.” A few participants commented that they are more aware of the onset of brain fog or automatic behaviors “when not too sleepy.” As one participant described, “[W]hen my sleepiness.... gets past a certain level, I lose insight that I’m really in trouble.” One web participant made a distinction between automatic behaviors and a sleep attack: “I sometimes just lose blocks of time, and figure I was doing automatic things, not awake or asleep.”

Participants generally commented that their onset of EDS symptoms occurred before the onset of other symptoms, slowly and mildly in some cases and more immediately and severely in others.

Cataplexy

As mentioned, cataplexy does not affect every person with narcolepsy. However, those who commented on their experience with cataplexy described the symptoms as frustrating, embarrassing and, at times, terrorizing. In-person and web participants described slackening of the jaw, weak knees, paralysis, dizziness, falling, feeling unable to breathe, and passing out. The following examples reflect the experiences shared:

- “It feels like I am awake inside a corpse. I am completely conscious, and I am completely unable to move anything, even a toe. The milliseconds or minutes that go by feel like an eternity.”
- “I often describe [cataplexy] as feeling like a puppet where all the puppet strings have been released, without warning.” (a web participant)
- One mother described her son’s cataplexy as “a popping feeling in his body.” By show of hands, many participants agreed that the term ‘popping’ describes their experience, and several web participants also concurred with this description.

Participants described their cataplexy triggers, particularly laughing, but also anger and other extreme emotions. A few noted that they intentionally repress or avoid strong emotional stimuli, such as laughter, fear, stress, and anxiety, in an attempt to prevent an attack. Web participants also identified lack of sleep, heat, certain foods, being startled, swimming, and stress as triggers. Some participants commented that their attacks are rare or have decreased as they have learned to control them. However a few commented that their attacks have become more severe or frequent, with several cataplexy episodes a day.

Other symptoms

In addition to EDS and cataplexy, participants described a number of other symptoms that have a significant effect on their daily lives:

- Some participants described **hallucinations** and night terrors, stressing the “realness” of their hallucinations, for example “going in and out of dreams so fast” that it can be difficult to distinguish a dream from reality. A few described recurring hallucinations involving an attacker or “a dark being.” One participant described the “adrenaline” effects after waking from a hallucination.
- Some participants reported suffering from insomnia, fractured sleep or other **problems falling or staying asleep**. For instance, one participant noted that during periods of worsened symptoms that, “... 45 minutes is a good night's sleep [and] two hours is fantastic.” Conversely, a few in-person and several web participants described sleeping for 12 or more hours a night or having extreme difficulty waking in the morning.
- A few participants described the effect of **chronic sleep deprivation** (“like you haven’t slept for 3 days), including feeling physically ill and having “an uneasy creepy feeling in your stomach.”

- A few participants described **sleep paralysis** as the inability to physically wake up from sleeping, as one participant explained being “aware but unable to move.” One participant commented that his attacks have been described as looking “like a mild seizure.” One participant described the dual effect of hallucinations coupled with sleep paralysis.
- A few participants commented on **general fatigue, lack of energy or reduced physical ability**. For example one participant commented: “I used to do a 5k every day... now I have to leave for class early so I don’t have to walk quickly.” A few participants commented specifically on feeling fatigued after a shower.
- Some participants associated **significant weight gain** with their narcolepsy, primarily because of its impact on their ability to exercise and stay active. One participant described “an insatiable desire to eat sugar and carbs,” while another commented that her impulsive eating habits are a mechanism to stay awake. Another believed that narcolepsy has slowed his metabolism.
- A few participants stressed the importance of acknowledging **depression** as an important secondary effect of narcolepsy. A few participants described having clouded judgment or suicidal thoughts brought on by depression, and one participant described being “admitted to multiple psychiatric units.”
- In-person and web participants also identified muscle tension, body aches upon waking, effects on mood or ability to manage emotions, headaches, seizures, homeostasis, loss of ocular muscle control, injury from falls, and problems with behavioral maturation. Several commented on having co-morbid conditions, such as fibromyalgia, gluten intolerance, and digestive issues.

Experiences with symptoms changing over time

Participants were asked to describe how their narcolepsy and its symptoms change over time. Participants identified an apparent cyclical nature of their symptoms, particularly with respect to their ability to sleep. One participant commented on annual cycles related to season changes and by show of hands, many participants agreed. As one participant commented, “I feel like my body is controlled by the sun. When the fall comes ... my body wants to sleep when it gets dark, and my body wants to awake with the sun.” A few participants described lunar, menstrual, or monthly cycles. A few commented that they cannot explain the cause of their cyclical symptoms. Participants also identified a variety of factors that they believe can trigger an exacerbation, including stress, anxiety, sleep deprivation, and being hot or dehydrated (e.g., from sun or exercise).

Some participants commented that their symptoms, even when treated, have gotten consistently worse over time or that they have developed new symptoms, such as cataplexy. As one participant explained, “before, naps would refresh me for short periods of time, but now, even on medication, I feel like an alert zombie.” One participant commented that her symptoms worsened perimenopause, and another commented generally that her symptoms, particularly homeostasis, have worsened as she ages.

Perspectives on the overall impact of narcolepsy on daily life

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

- **The significant, often debilitating, impact on work and school.** Participants cited EDS, in particular sleep attacks and cognitive effects, as significantly impeding their ability to follow along in class, stay focused, engage with co-workers or clients, or perform duties required of their jobs. Many participants described being fired, being urged to leave school, or giving up on their desired career.
- **Difficulty caring for themselves and their families.** Participants described “constantly going around in circles” trying to find keys, worrying whether they locked the door, setting timers so as not to spend too much time getting dressed or eating, and using sticky notes to remember where they are going. One participant described her guilt for not having the energy to bake or clean her house: “I used to beat myself up ... [w]hy can't I do more for my son?”
- **Decreased social interaction and impact on relationships** because of the challenges or embarrassment their symptoms present. Participants described avoiding social interactions for fear of exhibiting sleep attacks, cataplexy, brain fog, or other symptoms. A few described difficulty keeping plans because of unpredictable symptoms or of missing commitments that they had made without awareness. Participants said that these challenges over time have affected their relationships, as one participant described “[I have] lost contact with much of my family and friends.” A few described the strain that narcolepsy has had on their marriage, as one participant explained, [I am] unable to go for a night out, I don't want to sit and chat after dinner, I am too tired. We go to bed in separate rooms so that I receive optimal sleep.”
- **Stigma and being labeled by** supervisors, teachers, health care professionals, and others, as antisocial, lazy, careless, faking, unmotivated, and incapable. As one participant explained, “I'm often treated like a child because of [the cognitive effects].” Participants also commented on being accused of lying, or of being on drugs. A few commented that this effect is one of the biggest frustrations they face with narcolepsy, as one web participant described “being an intelligent individual, but being perceived as much less than so.” Participants described hiding the truth of their condition or their symptoms for fear of consequences.
- **Fear for their safety.** For example, one participant described “not allowing myself to cut vegetables or do anything dangerous.” Another participant said: I'm with [my wife] almost all the time because if I'm not there, she's afraid that her safety net is gone.”
- **Living for years without answers.** Many participants described their struggles living with no diagnosis or misdiagnosis (e.g., psychiatric illness, seizures) for years. Participant stressed the significant emotional toll of living without a diagnosis or with a misdiagnosis. For example, one participant explained her relief when finally realizing that “I finally had a label [narcolepsy diagnosis] because I wasn't mentally ill, I wasn't having a stroke, and [narcolepsy] is why I was sleeping.” (Comments on diagnosis and treatment of narcolepsy are revisited in Topic 2.)

- **Other impacts**, including decreased ability to partake in physical activities, reading and other hobbies, inability or reduced comfort with driving, inability to join the military, and significant financial impacts.

Discussion Topic 2: Patient Perspectives on Treating Narcolepsy

The second topic focused on patients' experiences with therapies used to treat their condition. Five panelists provided comments to start the dialogue; four were patients with narcolepsy and one was a parent of a child with narcolepsy. Panelists shared their experiences with complex and often trial-and-error treatment regimens, including prescription medications as well as napping and other lifestyle changes. The panelists described their struggle in finding long-term effective and tolerable therapies that can help them lead normal lives. They also described the choices they face in taking medications that have dramatically improved their narcolepsy symptoms but also present side effects that have a negative impact on daily life.

In the large-group facilitated discussion that followed, 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. Throughout the discussion, participants described in rich detail the benefits and the downsides they have experienced from prescription medications and a range of other therapies and modifications they use to manage their condition. Their perspectives on the benefits and downsides of these therapies, focused primarily on drug treatments, are summarized below. This section ends with participants' perspective on ideal treatments for narcolepsy as well as other aspects in the treatment of narcolepsy that they believe are important to consider.

Experiences with prescription drug therapy

According to polling questions, almost all in-person and web participants reported taking or having taken a prescription medication to treat their narcolepsy symptoms, including, Xyrem (sodium oxybate), Provigil (modafinil), Nuvigil (amodafonil), Ritalin (methylphenidate hydrochloride), amphetamines (including Adderall), antidepressants (no particular brand names were specified), and Lyrica (pregabalin). A summary of their comments is below.

Xyrem (sodium oxybate)

Xyrem, a depressant that is FDA-approved for the treatment of narcolepsy, received the greatest attention during the discussion. Some participants called it 'a wonder drug' and 'a miracle', as one stated, "without Xyrem, I'm not functional." Many web participants also highlighted the positive impact Xyrem had on their life, including one participant who said that "Xyrem [is] not perfect but without it, my 14-year-old son would have very low quality of life." A few participants cited the improvement of Xyrem over their previous options, as one participant described "there is a huge difference in the feeling of [having one's sleep architecture improved with Xyrem] rather than just being sedated and out cold for a couple of hours." Specific benefits included a decrease or elimination of cataplexy, sleeping through the night, and waking in the morning feeling well rested.

Participants who had experience with Xyrem noted the specific side effects that they have experienced, including extreme drowsiness falling asleep, feeling and acting "like you are intoxicated", automatic behaviors, involuntary movements, and muscle cramps. For example, one participant commented on

experiencing a chronic nightly “zombie-like state” resulting in sleep-eating (e.g., “a frozen loaf of bread”) that leads to illness the next morning and significant weight gain over the long term. This participant described taking the drastic measure of “barricading me in my bedroom, which is both dangerous and very concerning...” Additional effects identified by web participants included memory problems, anxiety, acid reflux, dry eyes, and dehydration. A few participants commented on the challenges associated with Xyrem's dosing regimen, which requires a second dose to be taken in the middle of the night.

Many participants spoke of the difficulty balancing the tradeoffs of the benefits and risks of Xyrem. As one described, “It’s at the point where you’re at one end [functioning at a much higher rate than before] or the other [problems caused by side effects].” A few participants described having, reluctantly, to stop taking Xyrem because of the side effects they experienced. As one participant said, “[when] my doctor told me to stop taking Xyrem immediately [because of involuntary movements] I was crestfallen. Even with that [side effect], it was still the best I’ve ever felt waking up.” One web participant said, “My family hates Xyrem [because of the sleep-eating and sleep-walking side effects], but for me the risk [is] something [I’m] willing to take for the reduction of cataplexy symptoms.”

Provigil (modafinil), Nuvigil (amodafonil), and other stimulants

Nearly all participants who took part in the polling questions (Appendix 3, Q7) indicated that they have used modafinil, amodafonil, methylphenidate, or amphetamines to treat their narcolepsy. Participants shared a range of perspectives on Provigil and/or Nuvigil. Some commented that the treatments worked most of the time, and others reported minimal symptom relief. A few participants noted intolerable side effects, including auditory hallucinations, an inability to rest, feeling “like I had toothpicks holding my eyelids open 24 hours a day, 7 days a week”, and increased heart rate. As one participant described “I was immediately started on Provigil and I felt amazing... But within three weeks I noticed I was getting short of breath. I could no longer go up a single flight of stairs without gasping for air at the top.” This participant further described similar effects with Nuvigil and how adding a heart medication has helped to control her heart rate. Many web participants who took either of these therapies also described side effects, including chest pains, anxiety, increased heart rate, decreased libido, teeth grinding, and jaw soreness.

Some in-person and several web participants described their experiences with Ritalin, Adderall, and other stimulants. A few commented on taking stimulants for many years. Participants described mixed results with these medications, ranging from those who rely on them for everyday functioning, to those who stopped taking the drugs because they were unable to tolerate the side effects. Side effects discussed included shaking, dry mouth and dental issues, and addiction issues.

Antidepressants

Although they were not discussed at length during the meeting, over half of participants who responded to the polling questions indicated that they take or have taken antidepressants as a part of their therapy. An FDA panelist asked participants if they used these medications with the intent to treat depression or to help them sleep. Responses were mixed; some participants said that they took them to directly treat depression and others, including a few web participants, said that they use these drugs to aid sleep or to relieve cataplexy symptoms.

Perspectives on the downsides of drug therapies

As indicated above, many participants stressed the important benefits that their narcolepsy treatments currently provide, which allow them to function and engage in society. Despite these many benefits, participants noted that even the best of therapies still make it very difficult for most patients to live with narcolepsy. Below is a summary of the challenging aspects of various treatments participants shared during this meeting.

- As captured above, participants described **significant side effects** of their specific therapies. In addition to the side effects already mentioned, headache, swelling, dizziness, changes in appetite, and weight loss or gain, were mentioned. Many participants described having to learn to control or live with these side effects. Others commented that the intolerability of the side effects precluded them from using particular medications.
- Some participants commented on the challenges dealing with a **complex medication regimen**, including the need to take one medication to control the effects of another medication. A few participants also raised concern about drug-drug interactions.
- A few participants commented on the **loss of effectiveness or “increased physiological tolerance” over time**. One participant noted that “despite being on the highest dose allowed for two different medications, my daughter’s narcolepsy symptoms are starting to change...” Another described taking “a weekly drug holiday to continually fight the problem of tolerance.”
- A few participants noted that there are no FDA-approved drugs specifically approved for pediatric use and commented on specific challenges for children (e.g., swallowing large pills).
- Many participants discussed **treatment cost** as a significant downside. As one participant commented, “\$500 per month is the difference between keeping their electricity on or taking their meds.” One web participant said “I could not imagine going back to life pre-Xyrem, but with insurance constantly fighting the ever increasing prices, I am in a constant state of worry.” A patient-advocate participant stated that “people are documenting that they are being charged over \$10,000 a month for Xyrem. That’s the dark side of orphan drug status...”

Perspectives on non-drug therapies

This meeting reiterated the important role that non-drug therapies have in helping narcolepsy patients manage their condition. According to the in-person and webcast polling results, nearly all participants utilize naps as a means to control their symptoms. Dietary modifications, exercise, counseling and support groups were each reported by more than half of participants. Almost half of participants reported using some other therapy not mentioned. Only a few participants polled said they used nothing other than drug therapy. A summary of their input on non-drug therapies is provided below:

- Participants generally viewed **naps** as fundamental to keeping their condition under control. As one described, naps are “not something voluntary, but necessary.” One participant described her daughter’s naps as having “priority over playing... because missing a nap means she will sleep more the next day, sometimes 18-20 hours.” Some participants, however, stressed that naps should be viewed as a *symptom* of their condition rather than as a treatment. For example, one participant, whose wife requires multiple 2+ hour naps a day, wondered “at what point

does a nap stop being a therapy and start being just part of the problem?” Participants also described their struggles within “a society [that] is not very nap-friendly,” particularly schools or workplaces that do not accommodate naps or allow sufficient flexibility, because, as one participant stated, “between 10:00 and 10:30 [strictly, every day] ... doesn’t work.”

- Many participants commented on the importance of **exercise**. They explained, however, that their symptoms make exercise difficult to sustain. For example, one participant said, “Exercise is always helpful, but it's really hard when you're always exhausted.” Some participants said that their quality of life improved with exercise, but not their specific narcolepsy symptoms.
- Many participants described making **dietary changes**, and a few commented that these changes have “made a huge difference.” As one participant described, the gluten-free diet “has helped me feel like I have not been hit by a Mack truck when I wake up.”
- A few participants described taking **vitamins and dietary supplements**, such as magnesium, omega-3, and B complex to address cognitive effects.
- A few participants commented on using **massage or acupuncture** to address muscle aches and tension associated with fatigue.
- Many participants described **coping or adaptation methods** they have learned to employ, such as avoiding certain stressful situations, adding as much flexibility to their day as possible, and investing in a high quality bed. For example, one participant described “going into self-employment [which] allowed me to sleep in my business... I had a sofa in a back room.”

Perspectives on ideal treatment for narcolepsy

Although participants clearly appreciated the treatment options that are available, they stressed the on-going need to enhance the treatment armamentarium, given current challenges with variability in effectiveness, tolerability, and access to available treatments. As one participant commented, they don’t want narcolepsy to “control” them, but rather they want to control their narcolepsy. Participants offered a range of specific improvements that they would like to see in treatments, described below:

- Many participants comments on specific aspects of their narcolepsy that they wished were better addressed, especially EDS, cataplexy, brain fog, and sleeping through the night.
- Some participants commented on the need to better understand and target the underlying cause(s) of the disease, for example orexin or hypocretin loss. A few commented that sodium oxybate targets the underlying cause (sleep consolidation) but that other options are needed for patients who cannot take sodium oxybate. Several web participants echoed this perspective.
- Some participants stressed the need to better address the significant side effects. Suggestions include finding different formulations and having a wider range of available therapies to choose.
- A few participants commented on wanting “medications approved for children and teenagers” that are more tailored to children (e.g., smaller pills).
- A few participants reiterated the need for treatments that are more accessible and affordable, a perspective that was repeated several times by web participants.

Other considerations on treating narcolepsy

- Throughout the meeting, many participants stressed the importance of recognizing the challenges people with narcolepsy face in getting **proper diagnosis and treatment**. Some expressed frustration with health care professionals who are unaware or fail to recognize the condition and its seriousness. A few participants offered specific examples, like having “to videotape the cataplexy since doctors didn’t believe there was anything wrong,” or being “treated for epilepsy for about six months.”
- Some participants commented broadly their view on the **lack of support** for children with narcolepsy at school, including medication plans, “504” education plans and support for standardized tests. A few web participants said that while school support for their children was essential for academic success, more needed to be done to help children fit in socially. Similarly, many participants highlighted the need for improved workplace acceptance.

Summary of Comments Submitted to the Public Docket

FDA received 175 comment submissions to the public docket that supplemented the September 24, 2013 Patient-Focused Drug Development meeting. The majority of comments were submitted by patients or parents of children with narcolepsy. FDA also received results from a survey conducted by Unite Narcolepsy, referred to in this report as the Unite Narcolepsy survey.

Overall, the comments received in the docket reflected the experiences and perspectives shared at the September 2014 meeting. They further elaborated on several issues raised during the meeting. The following is a summary of comments provided on narcolepsy 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 narcolepsy

The docket comments emphasized the chronic and debilitating nature of narcolepsy, the significant impact it has on patient’s lives, and the difficulty patients have treating their condition. The symptoms described were generally consistent with the symptoms raised at the meeting. Each of the following symptoms was mentioned by more than 30 commenters: excessive daytime sleepiness, general fatigue and lack of energy, cognitive impairments, cataplexy, hypnagogic hallucinations, and insomnia. The results of the Unite Narcolepsy survey generally appear consistent with input received from the docket.

Below are highlights of a selection of frequently mentioned symptoms.

- **Excessive daytime sleepiness (EDS)** was the most frequently mentioned symptom. Commenters reiterated the most severe aspects of EDS, including constant sleepiness, no control over falling asleep or waking up, and automatic behaviors such as sleepwalking or sleep-eating. As one commenter put it, “Narcolepsy causes me to have a sometimes uncontrollable urge to sleep. It has nothing to do with the amount of sleep or activity that I have.”

- Many commenters emphasized the burden of **general fatigue and lack of energy**. This was described by most as a combination of being easily fatigued by physical activity and feeling exhausted or sluggish at all times. Symptoms were often described as unpredictable or sudden. One commenter described her daughter’s experiences as follows: “One day she will feel “ok” and the next day she will be exhausted.”
- Others highlighted **cognitive issues**, such as difficulty with memory or concentration (also referred to as “brain fog”), as their most significant symptom. Commenters described difficulties learning and retaining new information, being unable to articulate thoughts, experiencing confusion, and general mental fatigue.
- **Cataplexy** was also among the most commonly mentioned symptoms in the docket and in the Unite Narcolepsy survey. Commenters’ descriptions of cataplexy were similar to those provided during the meeting, focusing on the severity of this effect, its significant burden on daily life, and the various triggers that could set off a cataplexy episode, including laughter, physical exertion, strong emotions, and stress.
- **Hypnagogic hallucinations** were mentioned frequently in the submitted comments. One commenter described a typical episode, saying “I feel that I’ve woken up in bed, and see and hear an intruder in a dark robe coming at me, stretching out his arms to strangle me. I can feel his hands on my neck but I cannot move a muscle to react. I’m frozen physically, as if wearing a strait jacket. These experiences are as real as reality to me, and utterly terrifying.” Several participants linked **sleep paralysis** to their hallucinatory episodes, often experiencing both symptoms simultaneously.
- Problems related to **insomnia and sleep dysfunction** were also reiterated several times in the comments. Several commenters described the irregularity of their nighttime sleep issues, including one person who said “I might sleep for 20 hours one day and then not be able to sleep for 2 days.” Others described difficulties waking in the morning, staying asleep at night, and not feeling refreshed or restored by sleep.

Submitted comments on the overall impact of narcolepsy on daily life

The docket comments reflected the input received during the meeting on the debilitating impact that narcolepsy has on patients’ daily lives, and the significant social, emotional, and financial toll the disease has on patients and their families. In addition, almost all of the respondents to the Unite Narcolepsy survey emphasized the significant and often debilitating impact on their professional life, their families, and their personal life.

- Most commenters emphasized the impacts on **social or family life**, including difficulties taking care of children, planning social activities with friends, and being able to reliably spend time with others. As one commenter said, “[Because of my narcolepsy symptoms], I must prioritize my time very carefully to make sure that I am able to get done the most important things in my life. Often times, this means skipping out on social occasions with my boyfriend, friends, and family members.”

- Several commenters stressed the **impact on professional life**, including not being able to find employers who understood or were willing to accommodate their health needs and feeling stigmatized by coworkers and supervisors.
- Many commented on the impact of their inability to participate in **basic activities, particularly driving**, due to either their narcolepsy symptoms or the side effects of the medications they take to treat those symptoms.
- Several commenters also reiterated patients' concerns regarding **inadequate medical care and treatment cost**. This included difficulties finding doctors who understood their condition, difficulty being prescribed helpful medications, and difficulties affording existing medications.

Submitted comments on current treatments for narcolepsy

The submitted comments reflected the challenges of managing the many symptoms of narcolepsy, while making difficult decisions about treatments. The range of commenter's experiences were similar to those at the public meeting in terms of prescription drug use, their use of non-drug therapies, and the side effects that were most significant or burdensome to them. The prescription drug therapies mentioned most frequently (40 or more mentions) were Xyrem, Provigil, Nuvigil, and other stimulants (including Ritalin and Adderall). Less commonly mentioned were non-drug therapies, such as avoiding gluten or changing diet, proper sleep hygiene, naps, exercise, vitamins and supplements, and acupuncture.

Commenters' experiences with prescription drug therapies emphasized the variability of benefits and side effects for different patients, and more detail is provided below. Comments related to non-drug therapies closely resembled input received during the meeting and are not revisited here.

- **Xyrem (sodium oxybate)**: Commenters' experiences with Xyrem were the most widely diverse of any of the treatments mentioned. Some described Xyrem as a "miracle drug," controlling many of the symptoms of narcolepsy. As one commenter said "With Xyrem, I feel like I function almost like a person without narcolepsy. I can't imagine what I would do without it." Others, however, reported little benefit and were troubled by significant side effects, including automatic behaviors, dry eyes and dehydration, hallucinations, and drowsiness. Several commenters also said they felt "dependent" on Xyrem, for example, needing to schedule their sleep around it, and feeling like they were not in control of their lives.
- **Provigil (modafinil) and Nuvigil (amodafonil)**: Commenters taking either of these medications reported a range of experiences with them, including some who reported feeling more alert, experiencing less sleep attacks, and generally finding it easier to stay awake. Others said that the treatments had little impact on their ability to function, including one person who said "The alertness achieved by taking modafinil feels 'fake'. The sleepiness is still there, but my body is less inclined to give in. The sleepier I am, the more 'forced' the alertness feels." Side effects were described similarly to those reported during the meeting, including chest pains, increased heart rate, and dental issues, as well as anxiety, rashes, and headaches.

- **Other stimulants, including Ritalin and Adderall:** Similar to other therapies mentioned, commenters had experiences with stimulants that reflected input received during the meeting. Several commenters reported significant benefits from these therapies, including one who said “When I started taking Ritalin I felt re-born. I could take care of my children, clean house and work outside the home without sleeping! [It] was wonderful.” Common benefits mentioned in the docket included increased alertness, energy, and stamina. Other commenters reported little or no benefit from these therapies. Common downsides included dry mouth, anxiety, dizziness, and increased heart rate.

Conclusion

This meeting was the fourth of the Patient-Focused Drug Development meetings. It allowed FDA to obtain patients’ in-depth point of view on the severity of narcolepsy, 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.

It is clear that narcolepsy 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 are grateful to patients, caretakers, and others who so thoughtfully and courageously shared their experiences and perspectives on narcolepsy. We truly admire the spirit of the participants, who demonstrated their fortitude in the face of adversity presented by their narcolepsy; perhaps best exemplified by one participant who shared during the meeting, “... I am so proud of myself.... in spite of the narcolepsy and in spite of life just chipping away at my self-esteem and having horrible feelings of self-doubt and being ashamed and embarrassed, I accomplished what I wanted to accomplish, and I can't tell you the stress... but I did it!”

Appendix 1: Meeting Agenda and Discussion Questions



Narcolepsy Public Meeting on Patient-Focused Drug Development



September 24, 2013

12:00 – 1:00 pm	Registration
1:00 – 1:05 pm	Welcome Soujanya Giambone, MBA <i>Office of Strategic Programs (OSP), Center for Drug Evaluation and Research (CDER), FDA</i>
1:05 – 1:10 pm	Opening Remarks Ellis Unger, MD <i>Director, Office of Drug Evaluation I, CDER, FDA</i>
1:10 – 1:20 pm	Overview of FDA’s Patient-Focused Drug Development Initiative Theresa Mullin, PhD <i>Director, OSP, CDER, FDA</i>
1:20 – 1:30 pm	Background on Narcolepsy and Therapeutic Options Ronald Farkas, MD, PhD <i>Lead Medical Officer, Division of Neurology Products, CDER, FDA</i>
1:30 – 1:40 pm	Overview of Discussion Format Soujanya Giambone, MBA <i>OSP, CDER, FDA</i>
1:40 – 2:10 pm	Panel #1 Comments on Topic 1 Topic 1: Patients’ perspectives on disease symptoms and daily impacts that matter the most. A panel of patients and patient representatives will provide comments to start the discussion.
2:10 – 2:55 pm	Large-Group Facilitated Discussion on Topic 1 Patients and patient representatives in the audience are invited to add to the dialogue.
2:55 – 3:10 pm	Break
3:10 – 3:40 pm	Panel #2 Comments on Topic 2 Topic 2: Patients’ perspectives on current approaches to treating narcolepsy
3:40 – 4:25 pm	Large-Group Facilitated Discussion: Topic 2
4:25 – 4:55 pm	Open Public Comment
4:55 – 5:00 pm	Closing Remarks

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 excessive daytime sleepiness, cataplexy, 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, work and school performance, etc.)
- 3) How have your symptoms changed over time?
 - a) Do your symptoms come and go? If so, do you know of anything that makes your symptoms better? Worse?

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

- 1) What are you currently doing 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 lifestyle modifications.)
 - a) What specific symptoms do your therapies 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 therapies improve your ability to do specific activities that are important to you in your daily life?
 - b) How well have these therapies worked for you as your condition has changed over time?
- 3) What are the most significant downsides to your current therapies, and how do they affect your daily life? (Examples of downsides may include bothersome side effects, inconvenient dosing schedules, access issues, etc.)
- 4) Assuming there is no complete cure for your condition, what specific things would you look for in an ideal therapy for your condition?

Appendix 2: Patient and FDA Panel Participants

Patient Panel, Topic 1

- Kerry Lenzi – Patient
- Brandon Coonrod – Patient
- Fran Rosen – Patient
- Joseph Poplawski – Patient
- Carrie Bollino – Patient

Patient Panel, Topic 2

- Allison Greenstein – Patient
- LaShun Ray – Mother of patient
- Casey Thompson – Patient
- Sharon O’Shaughnessy – Patient
- Justin Green – Patient

FDA Panel

- Ellis Unger, Office of Drug Evaluation I, CDER
- Eric Bastings, Division of Neurology Products (DNP), CDER
- Ron Farkas, DNP, CDER
- Sally Yasuda, DNP, CDER
- Larry Bauer, Rare Disease Program, CDER
- James Bona, Office of Orphan Product Development, CDER
- Theresa Mullin, Office of Strategic Programs, CDER

Appendix 3: Meeting Polling Questions

The following questions were posed to in-person and web meeting participants at various points throughout the September 24, 2014, Narcolepsy Patient-Focused Drug Development meeting. Participation in the polling questions was voluntary. These results were used as a discussion aid only and should now be considered scientific data.

Demographic 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. Have you ever been diagnosed as having narcolepsy?
 - a. Yes
 - b. No

3. Are you:
 - a. Male
 - b. Female

4. Age:
 - a. Younger than 10
 - b. 11 – 20
 - c. 21 – 30
 - d. 31 – 40
 - e. 41 – 50
 - f. 51 – 60
 - g. 61 or greater

5. What is the length of time since your diagnosis?
 - a. Less than 5 years ago
 - b. 5 years ago to 10 years ago
 - c. 10 years ago to 20 years ago
 - d. More than 20 years ago
 - e. I'm not sure

Question for Topic 1

6. Of all the symptoms you have experienced because of narcolepsy, which do you consider to have the most significant impact on your daily life? **Please choose up to three symptoms.**
 - a. Cataplexy
 - b. Daytime sleepiness
 - c. Hallucinations while waking up or falling asleep
 - d. Sleep paralysis
 - e. Difficulty sleeping
 - f. Restless leg syndrome

- g. Activity while sleeping, such as sleepwalking
- h. Other symptoms not mentioned

Question for Topic 2

- 7. Have you ever used any of the following drug therapies to help reduce your symptoms of narcolepsy? (check all that apply)
 - a. Modafinil, armodafinil, methylphenidate, amphetamine
 - b. Anti-depressants (off label use)
 - c. Xyrem (Sodium oxybate)
 - d. Other drug therapies not mentioned
 - e. I'm not sure

- 8. Besides your drug therapies, what therapies have you used to help reduce your symptoms of narcolepsy? (Check all that apply)
 - a. Naps
 - b. Dietary modifications
 - c. Exercise
 - d. Counseling and support groups
 - e. Other therapies not mentioned
 - f. I'm not using any additional therapies

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

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 narcolepsy 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 narcolepsy below draws from various sources, including what was discussed at the narcolepsy Patient-Focused Drug Development meeting held on September 24, 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 narcolepsy. 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>.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> – Narcolepsy is a chronic disorder of the central nervous system characterized by dysregulation of sleep-wake cycles. – An estimated 1 in 2,000 Americans are affected by narcolepsy although many who are affected remain undiagnosed. – Symptoms vary from patient to patient and generally first appear between ages of 7 and 25 years. Symptoms include excessive daytime sleepiness, cataplexy, disturbed nighttime sleep, automatic behaviors, cognitive impairment, and difficulty concentrating. – Symptoms can have a substantial effect on ability to function at school, work or in the home and to engage in social situations. Patients report that these effects result in stigmatization and have negative impacts on their education, jobs, families, and relationships. – <i>Refer to the Voice of the Patient report for a more detailed narrative.</i> 	<p>Narcolepsy is a rare, chronic neurological condition. 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	<ul style="list-style-type: none"> – There are five FDA-approved drug treatments for narcolepsy including: <ul style="list-style-type: none"> ○ Provigil (modafinil) and Nuvigil (amodafonil) are stimulants indicated to improve wakefulness in adult patients with excessive daytime sleepiness. Side effects include headache, dizziness, insomnia, increased heart rate and, rarely, serious rash. ○ Xyrem (sodium oxybate) is a depressant indicated for the treatment of cataplexy and excessive daytime sleepiness. The drug is taken at bedtime followed by another dose 2.5 – 4 hours later. Side effects include drowsiness, respiratory depression, automatic behaviors, and hallucinations. The drug is available through a restricted access program, and is a Schedule III controlled substance. – Other prescription stimulants, depressants, and antidepressants are also used off-label. – Most patients include scheduled naps, diet modification, 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 narcolepsy; 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>