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Narcolepsy Meeting Focuses On Symptoms, But Some Urge Attention To Underlying Cause

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Excessive daytime sleepiness, interrupted nighttime sleep and “brain fog” are key symptoms that new drugs developed for the treatment of narcolepsy should target, patients told FDA Sept. 24.

During a four-hour meeting held as part of the agency’s patient-focused drug development initiative, dozens of patients and caregivers talked about the daily struggle to cope with the symptoms of narcolepsy despite currently approved treatments.

The narcolepsy meeting was the first under FDA’s patient-focused drug development initiative to focus on a rare condition.

Although stimulants and sodium oxybate are widely used in the narcolepsy patient community, they are only partially effective in blunting the condition’s various symptoms, which can worsen over time. In addition, these therapies come with their own serious side effects which, for some patients, can make use untenable.

While FDA focused its questions for the meeting on the impact that narcolepsy symptoms have on daily living and what patients would like to see in new narcolepsy treatments, some patients took a broader view, saying that new drugs should target what is believed to be the condition’s underlying cause rather than merely providing symptomatic relief.

A Rare Disease Meeting

The narcolepsy meeting was the fourth of 20 sessions that FDA will host under its patient-focused drug development initiative. The program was created in the 2012 reauthorization of the Prescription Drug User Fee Act and is aimed at systematically gathering patient input on the burden of a given disease, existing treatments and risk/benefit tolerance. FDA intends to use this information in its regulatory decision-making process, including evaluation of new

treatments and potential development of clinical trial endpoints and outcome measures.

The agency recently released a report from the first patient-focused meeting, an April 25 session on chronic fatigue syndrome/myalgic encephalomyelitis (*“Patient Voice” Report Puts Chronic Fatigue Symptoms, Treatments In Benefit/Risk Framework* – *“The Pink Sheet,” Oct. 7, 2013*). In June, FDA held meetings on HIV/AIDS and lung cancer. A fifth session on fibromyalgia is scheduled for Dec. 10.

Narcolepsy was among the 39 disease areas originally nominated by FDA as potential meeting topics (*“FDA Adds ‘Consultation Meetings’ To Patient-Focused Drug Development Effort”* – *“The Pink Sheet” DAILY, Sep. 23, 2012*). Its inclusion on the final list followed an intensive letter-writing campaign from the patient community (*“Narcolepsy Patients Hope FDA Attention Will Spur Drug Research, Shed Misperceptions”* – *“The Pink Sheet,” May 13, 2013*).

FDA said that of the four meetings held to date, the narcolepsy session was the highest draw. A total of 700-800 individuals either watched a live webcast of the meeting or attended the proceedings at FDA’s White Oak headquarters.

The numbers are all the more striking in that narcolepsy is the first meeting under the PDUFA V program to focus on a rare condition. Narcolepsy is estimated to affect more than 1 in every 2,000 people in the U.S., although only about one-third of those who have the condition are formally diagnosed, said Ronald Farkas, lead medical officer in FDA’s Division of Neurology Products.

The Federal Register notice announcing the meeting described narcolepsy as “a chronic disorder of the central nervous system caused by the brain’s inability to control sleep-wake cycles [that] is characterized by excessive daytime sleepiness, cataplexy, hallucination, and disturbed nocturnal sleep.”

While there is no cure, several drugs are approved to help manage symptoms. Among these are stimulants aimed at improving daytime alertness, such as **Cephalon Inc.’s Provigil** (modafinil) and **Nuvigil** (armodafinil), **Teva Pharmaceutical**

Industries Ltd.'s *Adderall* (mixed amphetamine salts) and **Novartis AG**'s *Ritalin* (methylphenidate).

Jazz Pharmaceuticals PLC's *Xyrem* (sodium oxybate) is a central nervous system depressant approved for cataplexy and excessive daytime sleepiness in narcolepsy. It is taken in two doses - the first given at bedtime, the second taken several hours later - to improve sleep. It is the sodium salt of gamma hydroxybutyrate (GHB), a so-called "date rape" drug that has been associated with seizure, respiratory depression, decreased consciousness, coma and death. As a result, it is available only through a restricted distribution program.

Farkas noted that the drugs most frequently used to treat narcolepsy symptoms are associated with a host of side effects. Stimulants can cause irritability, nervousness, shakiness, heart rhythm disturbances, upset stomach, nausea, nighttime sleep disruption and appetite suppression. Depressants such as *Xyrem* are associated with drowsiness, dizziness, breathing problems, depression and sleep walking. The side effects of antidepressants, which are used off-label, can include impotence, high blood pressure, heart rhythm irregularities, gastrointestinal problems, headaches and insomnia.

The Worst Symptoms

"Narcolepsy is rare, it's under-recognized, it's under-represented," Office of Drug Evaluation I Director Ellis Unger said at the outset of the patient meeting. "It's a terrible, devastating disease, and it's an area where we really wanted to understand better how you think about your condition, what's important to you. We want to hear directly from you in terms of how you experience the different symptoms of narcolepsy, how those symptoms affect your daily lives, and what you're looking for in terms of future treatments."

Unger asked patients to consider the one or two symptoms that they would most like remedied by a new drug.

Drawing on his days as a practicing physician, Unger said that "when I saw patients with complex diseases, I would basically say, 'Mrs. Smith, if we could fix one thing - I understand you have all these symptoms - if we could fix one thing for you, what would you like us to fix?' And then if we could get there, we might even get to ... 'What would be the second thing you'd like us to fix?' And that's a way to kind of focus on what's important, and maybe you might put that in the back of your head during this discussion and think about what's really important to you. What is it, for example, you cannot do in your life that you wish you could do and that a drug could potentially help you with?"

FDA officials heard testimony from dozens of patients and caregivers describing debilitating symptoms that have affected their ability to attend school, get a job, maintain employment, drive, participate in social activities, and care for themselves and their families. In a poll taken at the meeting, patients cited excessive daytime sleepiness as the symptom that had the most significant impact on their daily lives, causing them to fall asleep in class, at work or in their cars.

Fran Rosen described such bouts of daytime sleepiness as "not the kind of sleep that you have control over. It's like an invisible man comes and injects sodium pentothal in you, and you're asleep."

After daytime sleepiness, patients who responded to the polling question rated cataplexy - the reduction or loss of muscle tone causing physical changes - and difficulty sleeping at night as the next most impactful symptoms on their lives.

Julie Flygare suffers from severe cataplexy and described a full cataplexy attack as feeling "like I'm awake inside a corpse. I am completely conscious, and all I think is just move your toe, just move your finger, do anything. And nothing responds."

Patients also described getting only minutes, or an hour or two, of sleep each night for weeks, months or years.

"I have not slept longer than about two and a quarter hours since I was in my 20s," one female patient said. "To me, a miracle drug would be something that would allow me to sleep through the night."

Although not specifically listed in FDA's polling question about the most impactful symptoms, mental foggy or "brain fog" was cited by numerous patients.

"I also find that the foggy from being in a half-sleep state during my limited waking hours to be maddening," Joseph Poplawski said. "The foggy causes me to forget conversations or commitments that I have made. ... This has caused me a lot of problems over the last several years. People have decided that I'm unreliable or that I'm ignoring them or neglecting them or not honoring my commitments that I've made to them or others. Imagine the horror of waking up and looking at your phone and realizing you've had several lengthy phone conversations that you have absolutely no recollection of."

When asked what symptoms she would most like a drug to address, one woman responded, "If I could name two things, it would be 1) keep me awake, 2) get rid of the brain fog."

Patients also described occurrences of sleep paralysis, hallucinations and performing various activities while asleep. Numerous individuals said their symptoms tended to ebb and flow with seasons and lunar cycles, and some female patients also reported symptom changes tied to their menstrual cycle.

Current Treatments Widely Used

Among patients in the audience who answered a question on medication use to reduce symptoms, 100% said they take or previously have tried stimulants, while 71% said they have tried *Xyrem* and 64% said they have used antidepressants off-label.

Despite the high rate of use of drugs indicated for treating narcolepsy, many patients said they still experience significant symptoms that keep them from driving or performing other activities.

Casey Thompson said she jumped at the opportunity to take Xyrem. "For me personally, it's been my miracle. I hesitate to say that because I said that once to someone, and they said, 'Well then what's your problem?' I say it's a miracle to an extent, but I still battle."

They also described the downsides of approved treatments. Although stimulants can help decrease daytime sleepiness, they can cause increased heart rate and shakiness and also make it more difficult to sleep at night, necessitating the use of a depressant for nighttime sleep.

Sharon O'Shaughnessy said that although she felt great shortly after starting Xyrem, the drug caused her to have seizure-like movements while sleeping. When she notified Jazz, the company told her to stop taking the drug.

"I was crestfallen," O'Shaughnessy said. "Even with that hour of flailing, it was still the best I ever felt waking up. So for me and other people who can't take Xyrem, we really need a pharmaceutical option for fixing sleep architecture, rather than mere sedation."

Several patients said Xyrem is inconvenient to use because it must be dosed in the middle of the night. They also said the drug's price was a hurdle to treatment because it can cost \$6,000-\$10,000 a month for patients without insurance.

Focusing On Underlying Cause

While most of the discussion was about narcolepsy symptoms and treatment impacts, some patients sought to refocus the discussion on the condition's underlying cause

Moshe Turner has had narcolepsy without cataplexy for approximately 45 years. He said he wanted FDA to understand that what patients call narcolepsy "is only that group of symptoms which are the most visible physical manifestations of the underlying neurological condition." He took issue with FDA's description of narcolepsy in the meeting notice as chronic disorder of the central nervous system caused by the brain's inability to control the sleep-wake cycle. "This is absolutely not true. Narcolepsy is a neurological disorder of the brain caused by interrupted or unavailable orexinergic signaling," he said. Interruption or absence of orexinergic signaling has been found to highly correlate with dysregulation of a wide range of processes throughout the body, such as breathing, blood pressure, heart rate and the sleep-wake cycle, he said.

Orexinergic signaling is the focus of some narcolepsy drug development efforts under way. In January, **Reset Therapeutics** announced the award of a five-year cooperative agreement from the National Institutes of Health to develop orexin receptor agonists for treatment of narcolepsy. Such drugs are designed to mimic the effects of the orexin protein, which is deficient in most narcolepsy patients, and restore normal balance to the body's sleep-wake cycles, according to the company.

"Giving me drugs that keep me awake during the day or help me to sleep better at night is like giving me a Band-Aid," he said. "These drugs merely provide symptomatic relief at best. What narcoleptics need is a drug which, if it can't restore orexinergic signaling, will at the very least restore the proper function of these other systems." 