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Narcolepsy Patients Hope FDA Attention Will Spur Drug Research, Shed Misperceptions

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When FDA chose narcolepsy as one of the diseases for its patient-focused drug development initiative, the narcolepsy community was thrilled, not just because of the regulatory assistance the selection could eventually provide, but also because the designation reflects the success of an awareness effort by a fledgling advocacy group.

"It's huge for us," said Julie Flygare, who led the campaign to get FDA to select narcolepsy.

People who have the disease may not be diagnosed until 10 or 15 years after the onset of symptoms as the sleep disorder is not well understood by doctors or the general public. FDA's focus on the disease is a chance to educate people about its debilitating symptoms and garner support for further research.

A leading patient advocate for the disease, Flygare posted information about the initiative on her blog with a sample letter and instructions encouraging people to urge FDA to pick narcolepsy. She also spoke at a meeting the agency held in September to get input from the public about the 39 diseases it was considering for its initiative.

The narcolepsy community responded to her call for action. In an April notice announcing the 16 diseases it would take up in FY 2013 through FY 2015, FDA said that more than half of the 4,500 comments it received concerned narcolepsy, lung cancer and interstitial lung disease ("FDA's Patient-Focused Meetings: Round One Selections Include Diseases Broad And Rare" – "The Pink Sheet," April 22, 2013).

Under the FDA Safety and Innovation Act of 2012, FDA is required to hold 20 public meetings with patients over the next five years to get their perspective on specific diseases. The criteria FDA considered in making its selection included whether the diseases are chronic, symptomatic or affect functioning and activities of daily living and whether there are no or few available therapies.

Narcolepsy, a disorder in which the brain loses the ability to maintain normal sleep and wake states, is estimated to affect one in every 2,000 Americans, or about 200,000 people, but it is estimated that only about one-quarter have been diagnosed. The disease is characterized by excessive daytime sleepiness, cataplexy (muscle weakness or paralysis), hallucinations, and sleep paralysis (the inability to move or speak while falling asleep or waking).

Drug To Replace Missing Brain Cells At Least 10 Years Away

One issue that patients will be discussing with FDA is the need for new treatments. Although there are currently available drugs – including Jazz Pharmaceuticals PLC's *Xyrem* (sodium oxybate) and Cephalon Inc.'s *Provigil* (modafinil) and *Nuvagil* (armodafinil) – those products only treat the symptoms of narcolepsy.

Flygare noted these treatments have drawbacks and do not work for everyone. For example, she said it takes months for patients to feel the benefits of Xyrem and to adjust to the side effects of nausea and vomiting. Xyrem also requires life style adjustments since those taking it cannot drink alcohol and they must wake up in the middle of the night to take a second nighttime dose.

In addition, some people are intimidated by Xyrem's history as a so-called date rape drug. Eveline Honig, executive director of Narcolepsy Network, noted that one doctor in a rural area had been prescribing Xyrem to a young man but declined to do so once the patient went to college, citing his concern that the drug might be taken by others. Xyrem was approved in 2002 with restrictions on its use, which were later classified as a Risk Evaluation and Mitigation strategy. It is the only drug approved to treat cataplexy.

Among other narcolepsy treatments, the stimulants Provigil and Nuvigil can cause shakiness and other symptoms while Novartis Pharmaceuticals Corp.'s *Ritalin* (methylphenidate) and Shire PLC's *Adderall* (amphetamine/dextroamphetamine)can make people feel anxious.

Despite these side effects, the current treatments are highly valued by the narcolepsy community. In the last 10 years

they "have made huge improvements to quality of life," Flygare said.

One compound in development for narcolepsy is Aerial BioPharma LLC's ADX-NO5, now in a Phase IIb trial. FDA granted the compound an orphan drug designation last year. The compound is believed to work through the noradrenergic and dopaminergic pathways to treat excessive daytime sleepiness associated with narcolepsy.

Morrisville, N.C.-based Aerial expects to complete the 12-week, double-blind, placebo-controlled randomized trial in the second half of 2013 and to present results of the Phase 2a study at the SLEEP meeting in Baltimore June 1-5. The goal is to have 90 patients in the Phase 2b trial.

Aerial's Exec VP of Drug and Development Gary Bream said ADX-NO5 is chemically distinct from modafinil and amphetamines, which target the noradrenergic and dopaminergic pathways. He said it is too soon to know if it offers benefits over existing treatments. "We hope it will be an improvement," Bream stated.

Drugs that replace hypocretin "should be like insulin for patients with type 1 diabetes" – Stanford's Emmanuel Mignot

Researchers have discovered that narcolepsy with cataplexy is usually caused by the lack of brain chemicals called hypocretins or orexins, which stabilize the brain's regulation of sleep and wake states. Scientists are now seeking to develop drugs that stimulate and replace the hypocretin cells.

Reset Therapeutics Inc., based in Burlingame, Calif., is developing hypocretin/orexin receptor agonists for the treatment of narcolepsy under a five year cooperative agreement with the National Institutes of Health. The project began in September 2012 and runs through August 2017.

Emmanuel Mignot, director of Stanford University's Center for Sleep Sciences and Medicine, believes that replacing the missing brain cells would be the best treatment for those with narcolepsy.

"It should be like insulin for patients with type 1 diabetes," Mignot said in an interview with Michael Twery, director of the National Center on Sleep Disorders Research at the National Heart, Lung, and Blood Institute. But he noted that it will probably take 10 more years to develop a treatment.

In the NHLBI interview, which is posted on YouTube, Mignot explained that about 20% of the population has a genetic predisposition to narcolepsy. It is believed that when they get an infection their immune system mistakenly kills the cells that produce hypocretin.

A Voice Of the Narcolepsy Community

It typically takes several years for those with narcolepsy to receive a diagnosis and it is not uncommon for a diagnosis to take 10 to 15 years. According to the National Institute of Neurological Disorders and Stroke, in about 10% of cases, cataplexy is the first symptom to appear and can be misdiagnosed as a seizure disorder.

Flygare said people with narcolepsy don't talk about it because it is considered a joke disease and job discrimination is a big issue.

Flygare, 29, was diagnosed during her second year in law school. Her first symptom was cataplexy – her knees buckled when she laughed. Over time the cataplexy progressed to the point that during an attack she collapsed to the ground and was in a state of paralysis. She also experiences hynagogic hallucinations, vivid dreamlike experiences while falling asleep or waking, and at least once a day she has a sleep attack, which she describes as feeling like you haven't slept in 48 to 72 hours.

After Flygare was diagnosed with narcolepsy she began working with a sleep specialist at Harvard Medical School and subsequently created a video with him to help students learn how to diagnose the disease. She kept her diagnosis private throughout law school but after graduation she wrote an article for the Boston Globe and decided to become an advocate.

"I felt there was a cycle of misperceptions," Flygare said. "No one knows it is a serious condition, and if no one talks about it you can't change those misperceptions."

She started a blog, Rem Runner, in 2010 that is a primary resource for information about the disorder. It includes a series of short videos in which Flygare discusses different aspects of the disease and how to cope with it. The blog also provides information about ongoing research.

Flygare is also a member of NHLBI's Sleep Disorder Research Advisory Board, serving as a patient representative, and is a frequent speaker at meetings focused on narcolepsy and sleep disorders.

People with narcolepsy tell her she is the first person they have known to have the disease and reach out to her for advice. "Everyone feels so alone," Flygare said. While she

can't get coffee with a thousand people, she connects with them through her blog, Facebook page and her memoir, Wide Awake Dreaming: A Memoir of Narcolepsy, which was published in December.

The book recently won first prize in the 2013 San Francisco Book Festival biography/autobiography competition. It begins with the appearance of her first symptoms and concludes with her running in the 2010 Boston Marathon.

Since running the marathon she has become an advocate for the narcolepsy community. She will be attending FDA's meeting with narcolepsy patients, which is to be held sometime in or around September. In addition to talking about the variations of the disorder and the need for new medicines, she would like to convey the need for treatments to be approved for use in children.

Getting on FDA's radar has been a major accomplishment for those living with narcolepsy. "There is no one in Washington working for us. It took a great effort of the community coming together to be heard," she said. Being part of the agency's initiative "is a huge step forward for the future of narcolepsy and sleep research."