

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

Huntington's Disease

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Introduction

On September 22, 2015, FDA held a public meeting to hear perspectives from people living with Huntington's Disease (HD) about disease symptoms, the impact of HD on their daily life, and their experiences with 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/Drugs/NewsEvents/ucm451807.htm>

Overview of Huntington's Disease

Huntington's disease (HD) is a hereditary, progressive, and fatal brain disorder that causes a range of physical, mental, and emotional disabilities, including uncontrolled movements, loss of cognitive abilities, and behavioral manifestations. Each child of an HD parent has a 50% chance of inheriting the disease, and HD affects both genders equally. If a child does not inherit the HD gene, he or she will never develop HD and cannot pass it on to subsequent generations. It is estimated that there are over 30,000 symptomatic Americans living with HD, and over 200,000 individuals at risk of inheriting the disease.¹

The onset of motor symptoms can occur in adulthood or in childhood. Adult onset HD typically appears in people 30-50 years of age, but the age and clinical symptoms at onset can vary considerably. HD is characterized by psychiatric problems, mood changes, involuntary movements, poor coordination, slurred speech, and impaired judgment. Adults with HD survive approximately 15-20 years after symptoms develop. Juvenile HD is present in approximately 5% of cases and is characterized by psychiatric problems, changes in speech, stiff walking, and difficulty with tasks. In both cases, weight loss is a significant symptom that becomes harder to manage as symptoms progress.

There is no cure for HD, and current treatments attempt to reduce the symptoms of HD. Medications such as tetrabenazine, antipsychotic drugs, dopamine receptor blocking or depleting agents, neuroleptic drugs (used off-label), and antidepressants are used to treat various symptoms of HD. Supportive care, such as occupational or physical therapy, can also help individuals manage their symptoms. Complementary and alternative therapies are also a common component of HD treatment regimens. As symptoms progress, individuals become increasingly or totally dependent on others for care.

Meeting overview

This meeting provided FDA the opportunity to hear directly from patients, caregivers, and advocates about their perspectives on HD 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 HD. The questions for discussion (Appendix 1) were published in a

¹ Statistic from The Huntington's Disease Society of America: <http://hdsa.org/what-is-hd/>

[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 50 HD patients and patient representatives attended the meeting in person, and about 60 web participants provided input through the live webcast and polling questions. Based on their responses to the polling questions, in-person and web participants represented a range of experiences with HD. Most participants indicated having a family history of HD. One-third of in-person participants reported having been diagnosed 5-10 years ago, while another one-third of in-person participants reported that they or their loved ones had been diagnosed 10-20 years ago. Over 40% in-person participants were between the ages 31-50, and over one-third were age 61 or greater. Approximately 10% of in-person participants were younger than 30. There was a similar representation of respondents on the webcast. Although participants may not fully represent all of the population living with HD, FDA heard experiences and perspectives on HD and its treatments, across a spectrum of patient ages and lengths of time since diagnosis.

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 November 22, 2015. Over 100 docket comments were submitted to the public docket², the majority by caregivers, or other patient representatives.

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

<http://www.fda.gov/Drugs/NewsEvents/ucm451807.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 HD symptoms, impacts, and treatment experiences reflect the words used by in-person participants, 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.

² A *docket* is a repository through which the public can submit electronic and written comments on specific topics to U.S. federal agencies such as FDA. More information can be found at www.regulations.gov.

The input from the meeting and docket comments underscore the diversity in patients' experiences with HD, the debilitating side effects of treatment, and the physical, emotional, and social impacts the disease can exert on patients' lives. Several key themes emerged from this meeting:

- HD is a devastating and debilitating disease that has a tremendous impact on patients and their families. Participants strongly emphasized that psychiatric and behavioral issues were the most significant symptoms of HD. A wide range of other symptoms were also described, including cognitive impairments, motor issues, depression, anxiety, and speech impairments. Many participants commented on the destructive impact of HD on multiple generations of their families.
- Participants said that current treatments do not adequately manage their most disabling symptoms. Participants commented that while some medications were effective in managing some symptoms, most treatment regimens were altered to add more medication or increase dosing as HD symptoms progressed. Nearly all participants said that they value the benefits they see in non-drug therapies, such as exercise, dietary modifications, lifestyle changes (to minimize stress), meditation, and prayer.
- HD impacts all aspects of patients' lives. Participants described severe limitations on physical activity, loss of independence and increased reliance on others for care, the devastating impact on relationships, and a constant fear of passing the disease onto their children. Participants shared that the cognitive impairments of HD often left them or their loved ones socially isolated, which worsened their depression and anxiety.
- Participants stressed the need for medications that are effective in delaying the onset of symptoms or slowing the progression of symptoms. Other participants emphasized the need for improved research on a cure for HD (including gene silencing therapies and stem cell therapies), faster clinical trials and drug development, and expedited drug reviews.

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

The first discussion topic focused on patients' experiences with their HD symptoms and the resulting effects on their daily lives. FDA was particularly interested in hearing about how specific symptoms manifest and have evolved over time. FDA was also interested in learning about the 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. They included: a mother speaking on behalf of her 10 year old son with Juvenile HD, a woman who was speaking on behalf of her two young adult sons (one who passed away, and one with late stage HD), a woman who spoke on behalf of her adult daughter who was diagnosed 16 years ago and had progressively worsening symptoms, a woman who was speaking on behalf of her 35-year-old husband with HD, and a 73-year-old woman who was diagnosed later in life.

The panelists' testimonies provided a vivid description of the burden of Huntington's disease. They described the challenges that they or their loved ones faced during symptom onset and progression,

their experiences with treatments, and the day to day consequences of living with HD. Panelists specifically highlighted in rich detail how their symptoms worsened over time, and the significant psychological, physical, and social impacts they have experienced because of their condition. As one panelist commented, HD affects “every symptom in my body.” 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. Participants emphasized that the most significant effects were primarily the result of the rapid progression of the disease.

Perspectives on most significant symptoms

In a polling question (Appendix 3, Q7), participants were asked to identify up to three symptoms that had the most significant impact on daily life. Cognitive impairment (such as difficulty concentrating and difficulty completing tasks) received the highest number of responses, followed by depression and anxiety, and unsteady gait/trouble with walking. Responding web participants reported similar impacts as most significant. The facilitated discussion provided insight into how symptoms manifest, and how they have changed over time; specifically, participants compared how symptoms were experienced upon diagnosis to how they experience these effects in the present day with advanced HD. The range of symptoms discussed by in-person and web participants is described below.

Cognitive Impairment (Including psychiatric behavior)

“The most significant symptoms of Huntington’s Disease are the ones you cannot see.” (in-person participant)

Over two-thirds of participants identified cognitive impairments as one of their most significant symptoms of HD. The cognitive impairments described took a variety of forms, ranging from memory loss or the inability to concentrate, to the loss of judgment and to violent or erratic behavior. This section describes the cognitive and psychiatric impairments that were discussed in greater detail.

The majority of participants stressed that **psychiatric problems** were the most significant manifestation of cognitive impairment. This included excessive anger, apathy or lack of emotion, irritability, aggression, physical violence, sexual hyperactivity, paranoia, hallucinations, delusions, compulsive spending, and erratic temperament. Several participants described their loved ones as getting “stuck on one topic.” One caregiver said that her son would get “locked on one thing for days, like telling me every 15 minutes for 30 hours straight that he couldn’t have an orgasm.” Caregivers commented that changes in behavior were often the first symptoms to manifest. The descriptions below illustrate the experiences shared in the discussion of psychiatric problems:

- “My son [with juvenile HD] was very combative, aggressive. You just couldn’t stop him. What he wanted to do was what he was going to do. One time...he just ran away to Paris at the age of 16, without me knowing about it.”
- “She [her late mother] became really aggressive towards me and my sister. She would fight us, physically, verbally. She was screaming at us...that she would hate us forever.”

- “[My son’s] lack of impulse control created bad situations, but his psychiatric issues caused violent reactions. He could not be reasoned with. His impulses resulted in unacceptable behavior, like leaving inappropriate messages on the CEO’s voicemail.”
- “These [psychiatric] symptoms have ripped my family apart, causing endless heartache and suffering. These symptoms took them [late family members with HD] away from us long before they died.”

Participants also commented on the **cognitive impairment** that they or their loved ones have experienced. Nearly all participants with HD or caregivers speaking on behalf of their loved ones were able to describe how cognitive impairment significantly worsened as HD progressed, specifically in their ability to focus or think clearly. The examples below illustrate these experiences:

- “[HD] changed my demeanor and behavior. I start losing control of situations and talking loudly. Now I lose patience with people who say that they're going to do something for me and don't. I also get angry with people that don't tell the truth, and I become stubborn if I feel I'm correct about something and somebody else is wrong.”
- “[My daughter, who once wanted to be an engineer] cannot even focus to read a newspaper today. Today she can't even write a grocery list, handle a monetary transaction, or help her son with homework.”
- “[My father] has a lot of...memory loss, can't remember a password that he has had that's the same for 20 years. He can't remember how to use the remote control some days. Making bad decisions, word-finding difficulties.”
- “[My husband’s and daughter’s] ability to focus and read declined...Carrying on conversations ultimately became very difficult, due to the delayed thought processes.”
- “[My son] had easily mastered all his honors math classes ... [but] by the time he was diagnosed, he could not subtract. Early on, he could no longer plan an activity, anticipate an outcome, or reason logically.”

Depression or Anxiety

Nearly half of in-person and web participants identified depression or anxiety as a significant symptom of HD. One participant observed that for her sister, who was diagnosed nearly 8 years ago, depression and anxiety brought on a “transformation” of her personality. One caregiver said that, “to see my husband, once so social, happy, full of life, sitting on a chair staring at a TV all day long is heartbreaking.” Many caregivers shared that depression or anxiety often led their loved ones to experience suicidal thoughts. Another participant shared that the ongoing worsening of symptoms and feeling “that I would never get better” led to significant depression. As one caregiver summarized, “fear of his ultimate fate plagues him.”

Chorea and Other Motor Symptoms

Participants explained in detail deteriorating motor symptoms, involuntary movements, and loss of body control. Participants described that motor symptoms manifested in a variety of ways including: finger and toe twitching, “randomly touching his head”, facial tics, facial chorea, rigidity, having trouble with or losing the ability to walk, tremors, “collapsing knee” and ankles, and a decline in posture.

Similar to psychiatric symptoms, participants observed that motor symptoms worsened as the disease progressed. In one example, a caregiver noted, “One Memorial Day, [my son] could swim fabulously. By Labor Day, he jumped in the pool and could not even tread water.” Most participants identified a significant loss of strength and balance as the disease progressed.

Participants also described other ways in which motor symptoms declined; they are listed below:

- “[My son] started kicking, kicking like a horse”
- “[At age 4] he walking on his toes [and had] stiffness in his arms, and changes in his handwriting”
- “My mother would basically try to eat her food, and while choking, she would be having a food fight with herself because of her chorea.”
- “The constant chorea movement wears her out to the point that it's an effort for her to even speak.”
- “Her poor balance plays an important part in what she can take part in. Crowded venues do not work. She falls into people.”
- “You spill food while you’re sitting at the table. I have to have a special lid on it [plastic drink cup] so I don’t spill stuff.”

Participants also described their experiences with dystonia. One caregiver said, “[My son’s] elbows take the brunt of the injury due to his dystonia and the way he holds his arms.” Some participants specifically provided comments on the triggers and effects of dystonia. In one example, a caregiver shared that when her son was agitated, his dystonia and chorea would worsen. She continued, “the dystonia was so bad, I couldn’t let him hold her [his baby cousin], because I was scared he would drop her. Telling him “no” triggered a seizure.” Another caregiver said that the combination of dystonia, muscle spasms, and poor balance “makes for a very rough, uncomfortable day and night” for her daughter.

Slurred Speech

Many participants observed that slurred speech or the inability to speak was a significant symptom that worsened as HD progressed. In one example, a mother said that her son lost the ability to speak by age 17 due to rapid progression of HD. One participant commented that her husband’s speech is so slurred that “you can’t even understand him.” In many cases, participants shared the need to interpret what their loved one was saying, as speech worsened. One caregiver shared, “A conversation that takes you

and [me] 30 seconds takes my daughter several minutes.” She continued, “I know the day will come when I will no longer hear her sweet, delicate voice. At times on the telephone, I need my grandson to interpret what she is saying, and that is frustrating for her and stressful.”

Other symptoms

In addition to the symptoms described above, participants also shared a range of other symptoms, as described below.

- Several participants identified **sleep issues** as a troublesome symptom of HD. Many participants explained that their loved ones experienced “days without sleeping”, irregular circadian rhythms, tossing and turning all night, or waking up several times throughout the night. In some examples, participants described other HD symptoms that triggered the inability to sleep. For example, one participant said that her insomnia was further exacerbated “due to the leg and arm movements and the restlessness that go with that.” Many participants commented that the lack of sleep resulted in severe fatigue the next day.
- Several caregivers commented that severe **neuropathy** was a painful and challenging symptom of HD. One caregiver explained how her son experiences neuropathy: “A few-minutes car ride is challenging for us due to his neuropathy. It causes so much pain and the pins-and-needles feeling that he gets all over his body. His neuropathy is partially kept at bay if he stands or walks.” She continued, “When it’s time for [him] to lay down, that is when his neuropathy is at its worst. He violently thrashes around on the floor, trying to itch while he is trying to go to sleep. He hasn’t slept in a bed in over two years because the bed is too soft. He said the hard surface for the itching makes it better, but the itching is still horrible.”
- Participants highlighted a range of **gastrointestinal (GI) issues** including: urgency, frequency, “extreme bowel” issues, esophageal and stomach ulcers, dilated esophagus, an increase in stomach or intestinal flora, and loss of appetite. One caregiver said that her daughter, who has juvenile HD, often “writhe[s] around in pain because of her stomach issues.”
- Other symptoms were also mentioned in the discussion of HD symptoms, including dental issues (such as dry mouth, lesions in mouth), hearing loss, and increased saliva production (leading to choking). One caregiver shared that her son’s “back has some scoliosis...and his ribs are pulling away from his sternum, so he has a rather large indentation in his chest.” Another caregiver noted that her daughter’s seizures were so severe that, “when her jaws clenched, her gums would bleed.”

Symptom variability and triggers to symptoms

In addition to discussing how symptoms evolved, participants provided detail about how HD symptoms changed hour-to-hour and day-to-day. One web participant commented that “symptoms can fluctuate, but they are always present and never fade.” In one example, a caregiver described, “one day...he [my husband] can walk fine, but his speech was way off. Another day, it would be the opposite.”

Participants pointed out that stress, changes in activity, changes in routine, and mood were triggers that affected symptoms. One caregiver commented on her father, saying “if he’s more agitated, we’re going

to see more symptoms that day. If he's more relaxed, you're not going to see nearly as many symptoms...he actually may look completely normal."

Overall impact of Huntington's Disease on daily life

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

- **The ability to perform activities.** Participants commented that the burden of HD left them or loved ones unable to perform many, if not all, activities. Participants described being unable to attend school, continue working, driving, performing household activities, eating (due to fear of choking), taking care of oneself, participating in favorite hobbies (such as biking, walking, playing on the playground), and completing simple tasks. One participant stated that "spontaneity no longer exists. Last-minute activities cause stress." Another caregiver shared that her husband "loved to be around people, and people loved being around [him]. Fast-forward to today. [He] is 35 years old...most days, he barely gets off the couch." One participant commented that slurred speech, hearing loss, and "thinking [that] no longer correspond[s] with my speech" resulted in her being unable to continue working as a pharmacist; she described this moment as being "very, very distressful."
- **Being dependent on others.** Nearly all participants noted that they or their loved ones have become increasingly or fully dependent on others for care, as HD symptoms worsened. One caregiver stated that her daughter needed assistance with "brushing her hair, teeth, bathing, dressing, having her food cut up...making decisions; it's depressing to lose that independence." Others also commented that their loved ones have become "bedbound and completely dependent" on caregivers. Participants noted the challenges of managing around-the-clock care, including finding a facility that could accommodate their loved ones. One participant explained that her mother did not realize that she needed help, sharing, "I would come home from work, and she would have fecal matter all over herself and her bedroom. She would not allow me to assist her. She...just didn't think there was a problem."
- **The impact on relationships.** Participants noted their challenges that HD symptoms posed on their relationships with others. One caregiver said that both of her sons' marriages ended early because of the "inability to contribute to or understand the relationship. Their behavior became too difficult for their wives." A mother commented that her son, who suffers from severe neuropathy and itching, has been unable to sit in a car to go see his father who was in a nursing home with end-stage HD. Another caregiver described that many of her daughter's friends have "faded away. People are uncomfortable seeing her like this. [She's] not the friend they remember." She continued that her eighteen year old grandson is "hesitant to have friends over because of his mother's condition."

Participants commented that the impact on relationships often left them or their loved ones feeling socially isolated. Many participants described that as motor symptoms worsened, the constant "stares, comments, and judgments" often led to anxiety and panic. Several participants noted that their loved ones were often mistaken by the public and law enforcement to be inebriated or acting inappropriately, due to a lack of understanding of HD symptoms. One caregiver stated that her son "retained the ability to process reality...he was fully aware of how people viewed him and what his future held. Given that people think HD

victims do not understand their surroundings, he was harassed and subject to disparaging remarks. As a result, he could not be around most people.”

- **Worry about the future.** Participants expressed significant worry, anxiety, and fear for the future facing the challenges of HD. A mother of a son with juvenile HD, shared, “[My son] tells me every day, ‘Mommy, I hate JHD’ and becomes very tearful – [it’s] very difficult, as his mom, to hear because it makes me feel helpless.” Many participants voiced their fear of the genetic aspect of HD, sharing, “I don’t know what’s been more terrifying for me, watching [HD] take everything away from my husband or knowing that our children have a 50 percent chance of inheriting their father’s fate.”

Topic 2: Patient Perspectives on Treatments for Huntington’s Disease

The second discussion topic focused on patients’ experiences with therapies used to treat their HD. Five panelists provided comments to start the dialogue: a caregiver who spoke on behalf of her loved one who had been diagnosed with HD 10 years ago, a 54-year-old woman who shared her experiences participating in clinical trials, a mother who spoke on behalf of her 21-year-old son who had been misdiagnosed early on, a caregiver who spoke on behalf of her late husband and daughter, and a caregiver who spoke on behalf of her husband and his experiences using technology to manage his HD symptoms. The panelists shared their experiences on not only the treatments they used, but how the treatment regimens changed as symptoms worsened.

In the large group facilitated discussion that followed, several of the 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 experiences with prescription drugs, medical procedures, non-drug and alternative therapies. Participants’ perspectives on the benefits and downsides of these treatments are summarized below. This section ends with participants’ perspectives on considerations regarding treatment decisions.

Perspectives on HD treatments

According to the polling question (Appendix 3, Q8), the majority of in-person and web participants reported using antidepressants and antipsychotic drugs, in addition to a range of other drug therapies. These therapies are discussed in further detail below:

Nearly all participants noted that they or their loved ones took a combination of **antidepressants and antipsychotic drugs** to manage their depression, anxiety, and psychiatric symptoms. One participant said that she takes Zoloft (sertraline) daily, adding “if I forget to take that, I am irritable, and the people around me notice.” Another participant noted that her husband takes trazodone, which “has worked, but not to the degree that it helps anymore.” Other antidepressants mentioned included Celexa (citalopram), Abilify (aripiprazole), Ativan (lorazepam), Klonopin (clonazepam), Remeron (mirtazapine), and venlafaxine. A few participants mentioned that Depakote (divalproex sodium) helped to manage “severe cognitive processing” and violent behavior. A mother said that after starting Depakote, her son’s violence “completely ended...he became very calm.” Other antipsychotic drugs mentioned included Zyprexa (olanzapine), Haldol (haloperidol), and risperidone.

Several participants commented on their experiences taking Sinemet (**carbidopa-levodopa**). One caregiver called Sinemet her son's "miracle drug", adding that it controlled his involuntary kicking and helped him to sleep. She said that dosing had started with one tablet upon diagnosis, and then increased to two tablets, three times a day, in six years. This caregiver also commented that as HD progressed into worsening chorea and dystonia, "sometimes, even the Sinemet doesn't help, and we have to give him pain meds in order to help him sleep and give him rest."

Other participants provided their experiences taking Xenazine (**tetrabenazine**) to manage HD symptoms (chorea). Several caregivers mentioned that tetrabenazine was effective in managing chorea and helped to "prolong independence" for their loved ones. One caregiver noted that tetrabenazine improved her partner's chorea, stating "he's now actually able to play with his son...which is amazing." However, participants also mentioned downsides of tetrabenazine, including depression, agitation, difficulty sleeping, "dulling" of personality, weight gain, and issues with perception. Web participants shared similar perspectives. One caregiver commented that despite the fact that tetrabenazine helped some symptoms, "it's not taking enough of his symptoms away to lead a ...normal life." Similarly, another participant described that as her mother's HD chorea worsened, tetrabenazine was no longer effective in controlling it. One participant said that she felt "so sick" on tetrabenazine that "it was not worthwhile for me to take."

Other prescription drug therapies mentioned included Namenda (memantine) for cognitive function, amantadine to manage rigidity, galantamine hydrobromide for memory, and Flomax (tamsulosin) for bladder control. One participant mentioned that verapamil helped to restore her "creative thinking abilities...and countered my apathy." A caregiver shared that her son has Botox injections in his salivary glands to "keep his saliva down...to keep him safe from aspirating."

Participants also provided their general perspectives on the effectiveness of treatments. One caregiver said that if her son misses a pill, "I know right away. He can't walk, he can't do anything by himself...he has a really bad day." Participants agreed that despite taking a combination of medications, treatment regimens generally only provide "minimal relief." One caregiver described that her partner's treatment regimen "makes the most significant symptoms of his disease better, but nowhere near a tolerable condition." The same caregiver shared that her partner's medications "have changed frequently over the years...every increase or new medication becomes overpowered by the disease." Participants agreed that as symptoms worsened, treatments often were modified or changed (for example, increasing dosages or changing medications). One mother described her son's "trial and error" treatment regimen, "it's just such a hunt-and-peck...what works and what doesn't? It's very maddening."

Medical Procedures

A few participants commented that their loved ones underwent medical procedures as part of their treatment regimen. One caregiver mentioned that her son with juvenile HD was scheduled to have a percutaneous endoscopic gastrostomy procedure due to the "increase in his chewing and swallowing difficulties." Another caregiver said that her husband received a fetal pig tissue transplant to replace damaged brain tissue. She added, "After four years of close observation and taking cyclosporine for possible tissue rejection, the [medical team] felt that the surgery neither helped nor harmed him."

Other Therapies

In a polling question (Appendix 3, Q 9), the majority of participants identified using a range of non-drug therapies to manage their HD symptoms. These therapies are described below:

- Many participants commented on the importance of **exercise or physical therapy** to manage their HD symptoms. Participants mentioned walking, running, biking, swimming, Qigong, and stretching. Many commented that they or their loved ones continued to incorporate exercise into their treatment regimen until their HD symptoms prevented them from being able to do so. One caregiver commented that her husband used a variety of technology tools, including Wii (to help improve his hand-eye coordination and balance) and Fitbit (to help monitor his steps and calories). She also said that her husband wears ankle weights to improve his muscles and uses osteopathic manipulative treatment to “relax his muscles and spasms.” Finally, one participant shared that she undergoes physical therapy to practice standing postures to “retrain my brain [to not give in] to the balance and gait problems.”
- Participants also noted that they incorporated **diet modifications** as part of their treatment regimen. These included: eliminating alcohol, caffeine, drugs, and tobacco; increasing the intake of antioxidants (such as blueberries), eating at least 5,000 calories a day, and using nutritional drink supplements.
- Other non-drug therapies included a variety of **dietary supplements** (such as Coenzyme Q10, fish oil, melatonin for sleep, multivitamins, creatine, and acai). A few participants noted the use of medical marijuana to manage their HD symptoms.
- A range of **other therapies** were mentioned including: meditation and prayer, support groups, getting sufficient sleep, and homebound education to preserve and promote independence. One caregiver commented on the importance of minimizing stress for her daughter. She shared, “She doesn’t need stress to compound her issues. We try to keep conversations and calm surroundings.” Another caregiver also mentioned that her husband uses a service dog to help “with balance. [The dog] also helps with picking [my husband] up when he falls.” This caregiver also noted that her husband used technology applications, developed by Oral-B to remind him on proper oral health, Lumosity.com for mental training, and Facebook “to still socialize with people that he’s had previously in his life...he enjoys that.”

Perspectives on ideal treatments for Huntington’s Disease

Participants provided feedback on what they would look for in an ideal treatment for HD, including participating in a clinical trial. Many participants shared that participating in clinical trials was “one of the best things for the treatment of Huntington’s Disease.” One caregiver said that being a part of clinical trials helped her sons feel “in control of things. It also gave them hope.” This comment resonated with many other participants. Another caregiver mentioned that her husband enrolled in trials not only for himself, but also “for our children.” In another example, a caregiver stressed the importance of improving on juvenile HD research and clinical trials, adding “these kids don’t have time to wait. We need to preserve their ability to think and to communicate so that they can tell us what’s wrong and how to help them.”

Outside of a cure, many participants wanted medication that could drastically slow progression of symptoms or delay the onset of symptoms. One participant commented that a slower progression of symptoms would mean “a better, more productive quality of life for a longer period of time. We would consider this a victory.” Others pointed to specific symptoms, such as slowing the onset of cognitive impairment, motor symptoms, and chorea. One participant commented on the need to identify or develop therapies that “can be given whether you’re at risk or you are gene-positive, very, very early, well before onset.”

Other aspects of ideal therapy included: developing drugs in gel capsule form that are easier to swallow, antidepressants with fewer side effects, and medication that is effective for longer periods of time. Participants also commented on the importance of developing and improving technologies for therapeutic use, including: alternative communication options to address speech impairments; newer technologies to identify biomarkers; and expanding research on gene therapy and gene silencing.

In addition to their perspectives on ideal therapies, participants throughout the day commented on other aspects that they believed are important to any discussion on HD healthcare, including: early and accurate diagnosis, fast tracking the approval of effective HD treatments, and approving medical marijuana.

Summary of Comments Submitted to the Public Docket

Over 100 comments were submitted to the public docket that supplemented the Patient Focused Drug Development meeting on Huntington’s Disease. The majority of comments were submitted by caregivers; some comments were submitted by patients and other patient representatives. One comment was submitted by an advocacy organization.

Overall, the comments received in the docket reflected the experiences and perspectives shared during the September 2015 public meeting. The following is a summary of comments provided on HD symptoms, impacts on daily life, treatments, and decision making around 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 Huntington’s Disease

Similar to what was heard during the public meeting, comments submitted to the public docket reemphasized the debilitating effect of HD. Many commenters said that the most difficult and “cruellest” aspect of HD was that it takes a once “normal healthy person and slowly dismantles them bit by bit, taking everything from them.” Docket commenters identified several unique symptoms of HD, which were all discussed during the public meeting. These include:

- Cognitive impairments, including psychiatric issues
- Speech impairments
- Dystonia
- Oral and dental issues, including choking
- Depression and anxiety
- Sleep issues
- Gastrointestinal issues
- Symptoms of neuropathy
- Itching
- Weight loss

Several commenters reiterated the complexity and difficulty of cognitive impairment, especially when manifesting as psychiatric problems. Commenters described psychiatric issues as “combative”,

uncontrollable anger, tantrums, “emotional meltdowns”, apathy, paranoid delusions, perseveration, and rage. Caregivers said that this behavior disrupted family dynamics and that “personality changes” overcame their loved ones. Similar to the public meeting, participants also described other ways in which cognitive impairments manifested, including difficulty completing tasks, inability to sequence or solve problems, memory lapses, confusion, and making decisions. Nearly all who commented on cognitive and psychiatric symptoms said that these were the most difficult symptoms to manage and live with.

A few commenters described motor effects. Commenters shared that their loved ones had severe movement issues and frequent falls. One caregiver described that dystonia left her loved one’s “internal organs displaced and resized from muscles restricting them.” Others mentioned painful and severe muscle spasms; one commenter stated that her daughter would grind her teeth “so bad, she has broken two of them”, and had chewed off “half of her tongue.”

A range of other symptoms were also noted. One caregiver mentioned impaired speech as “the most problematic, because as he gets worse and he slurs more, people don’t understand him and gets frustrated and angry.” One commenter described neuropathy as “24/7...nothing could relieve this pain.” Gastrointestinal issues mentioned included constipation, large bowel movements, and loss of appetite. Similar to the public meeting, commenters identified stress (mental, physical, or emotional) as the most significant trigger to exacerbate HD symptoms.

Submitted comments on the overall impact of HD on daily life

The docket comments reflected the input received during the meeting related to the debilitating impact of HD on patients’ daily lives, and its significant toll on patients and their families. Many commented that HD symptoms greatly limited the ability to perform any physical activity, including caring for one self, performing a job, participating in activities, or managing their household. Commenters described being unable to continue activities they once loved, such as traveling, walking, writing poetry, or being with friends, due to worsening cognitive impairments and motor issues. Caregivers mentioned that their loved ones had trouble eating and lived with a constant fear of choking as symptoms progressed.

Other comments reiterated the significant impact on personal and family life, including difficulty with family planning (due to the genetic nature of HD), loss of independence, and reliance on others for care. Commenters discussed that relationships were stressed or lost due to HD, often resulting in social isolation. As one commenter summarized, “[HD] doesn’t just affect individuals. It guts entire families, and the future of those families.”

Submitted comments on current treatments for HD

The submitted comments about experiences with treatments were similar to those expressed at the public meeting. Prescription drug therapies mentioned included antidepressants and antipsychotics, such as Lexapro (escitalopram), lorazepam, Risperdal (risperidone), Depakote (divalproex sodium), trazodone, Paxil (paroxetine), Zyprexa (olanzapine), and Namenda (memantine).

Several commenters described their experiences with Xenazine (tetrabenazine). A few commenters noted that tetrabenazine was effective in controlling chorea; however, one commenter said that tetrabenazine caused depression. One caregiver commented that her husband took Artane

(trihexyphenidyl HCl) to manage his dystonia. Most commenters noted that as symptoms worsened, dosages were often increased and medications were added to the treatment regimen. .

The majority of the comments submitted focused on experiences with non-drug. One commenter noted that exercise, such as walking and swimming, helped to manage chorea and other motor symptoms. Dietary modifications, such as avoiding alcohol, eating a Mediterranean diet, eating blueberries, and avoiding red meat were also mentioned. Other commenters said a range of vitamins and nutritional supplements that they or their loved ones used to manage HD symptoms including: B-12 complex, L-lysine, protein supplements, selenium, probiotics, fish oil, and coenzyme Q-10. Alternative therapies mentioned included acupuncture, massage, and meditation.

Over the counter therapies mentioned included Advil (ibuprofen) for headache and allergy medications. Other therapies mentioned included using a feeding tube for delivering nutrition, therapy dog, nicotine from cigarette smoking, and maintaining a routine sleep schedule.

Submitted comments on ideal treatments for HD

Several perspectives were provided on ideal treatments for HD. Aspects of ideal treatments included medications that could more effectively treat cognitive issues, speech impairments, and control movement issues. Others expressed the need for medications that could delay the onset of symptoms or slow the progression of symptoms. Many comments emphasized the need for furthering research into gene silencing and stem cell therapy (including induced pluripotent stem cell therapy). Finally, several commenters stressed the need for faster and more accessible clinical trials, and expedited drug approvals.

Conclusion

This Patient-Focused Drug Development meeting on Huntington's disease provided FDA the opportunity to hear from patients and caregivers first hand on the significant and debilitating impact that Huntington's disease has on their lives, over multiple generations. FDA recognizes that patients have a 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. As communicated by Dr. Billy Dunn during the opening remarks, FDA values the opportunity to hear firsthand the experiences of people living with HD and to incorporate this learning into the agency's thinking and understanding of HD.

FDA is profoundly grateful to the patients and caregivers who so thoughtfully and generously shared their personal stories of living with HD. Through this meeting, FDA learned what matters most to patients and caregivers regarding symptoms, impacts, and aspects of HD treatments. The participants' sense of community and their desire to advocate for future generations at risk for HD were strikingly clear. As one caregiver shared and so many others agreed, "I cannot protect my children from the genetic fate of Huntington's disease, but what I can do is fight for them."

FDA shares the patient community's desire and commitment to furthering the development of safe and effective drug therapies, to not only slow down disease progression, but one day, cure Huntington's disease.

Appendix 1: Meeting Agenda and Discussion Questions



Huntington's Disease Public Meeting on Patient-Focused Drug Development



September 22, 2015

8:00 – 9:00 am	Registration
9:00 – 9:05 am	Welcome Soujanya S. Giambone, MBA <i>Office of Strategic Programs (OSP), Center for Drug Evaluation and Research (CDER), FDA</i>
9:05 – 9:10 am	Opening Remarks Billy Dunn, MD <i>Director, Division of Neurology Products (DNP), Office of New Drugs (OND), CDER, FDA</i>
9:10 – 9:20 am	Overview of FDA's Patient-Focused Drug Development Initiative Theresa Mullin, PhD <i>Director, OSP, CDER, FDA</i>
9:20 – 9:30 am	Background on Disease Area and Treatment Dave Podskalny, MD <i>Medical Officer, DNP, OND, CDER, FDA</i>
9:30 – 9:35 am	Overview of Discussion Format Soujanya S. Giambone, MBA <i>OSP, CDER, FDA</i>
9:35 – 10:05 am	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.
10:05 – 10:40 am	Large-Group Facilitated Discussion on Topic 1 Patients and patient representatives in the audience are invited to add to the dialogue.
10:40 – 10:50 am	Break
10:50 – 11:20 am	Panel #2 Comments on Topic 2 Topic 2: Patient perspectives on current approaches to treating Huntington's Disease. A panel of patients and patient representatives will provide comments to start the discussion.
11:20 – 11:55 pm	Large-Group Facilitated Discussion on Topic 2 Patients and patient representatives in the audience are invited to add to the dialogue.
11:55 – 12:25 pm	Open Public Comment
12:25 – 12:30 pm	Closing Remarks Eric Bastings, MD <i>Deputy Director, DNP, OND, CDER, FDA</i>

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: ability to control movements, balance/coordination, difficulty concentrating, sleeping, mood/behavior 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 you need assistance because of your condition? (Examples of activities may include sleeping through the night, daily bathing/showering, cooking, eating, dressing, shopping etc.)
 - a) How do your symptoms affect your daily life on the **best days**? On the **worst days**?
3. How has 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. How has your condition affected your social interactions, including relationships with family and friends?
5. How has your condition affected your mood (for example; depression, apathy, patience/tolerance for frustration)?

Topic 2: Patients' perspectives on current approaches to treating Huntington's Disease

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 diet modification, 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, interacts with other medications, need to visit your doctor more frequently etc.)
4. Assuming there is no complete cure for your, what would you look for in an **ideal treatment** for a specific aspect of your condition?

Appendix 2: FDA and Patient Panel Participants

Patient Panel, Topic 1

- Colleen Walsh-Barnes – Caregiver
- Marie Clay – Caregiver
- Julie Rosling – Patient
- Denise Hudgell – Caregiver
- Katie Jackson - Caregiver

Patient Panel, Topic 2

- James D’Ambola – Patient (testimony presented by caregiver, Jessica)
- Karen Milek – Patient
- Stacey Sargent – Caregiver
- Cheryl Sullivan Staveley – Caregiver
- Karen Douglas - Caregiver

FDA Panel

- William Dunn (Division of Neurology Products (DNP), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER))
- Dave Podskalny (DNP, OND, CDER)
- Ellis Unger (Office of Drug Evaluation I, Office of New Drugs (OND), CDER)
- Eric Bastings (DNP, OND, CDER)
- Susanne Goldstein (DNP, OND, CDER)
- Kenneth Bergman (DNP, OND, CDER)
- Leonard Capcala (DNP, OND, CDER)
- Peter Komo (Division of Neurological and Physical Medicine Devices, Center for Devices and Radiological Health)
- Leu Xu (Central Biologics, Center for Biologics Evaluation and Research)
- Theresa Mullin (Office of Strategic Programs, CDER)

Appendix 3: Meeting Polling and Scenario Questions

The following questions were posed to in-person and web meeting participants at various points throughout the September 22, 2015, Huntington's Disease Patient-Focused Drug Development meeting. Participation in the polling questions was voluntary. The results were used as a discussion aid only and should not 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 Huntington's Disease?
 - a. Yes
 - b. No

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

4. Age:
 - a. Younger than 20
 - b. 21 – 30
 - c. 31 – 40
 - d. 41 – 50
 - e. 51 – 60
 - f. 61 or greater
 - g. Not applicable

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

6. Do you have a family history of Huntington's disease?
 - a. Yes
 - b. No
 - c. I'm not sure

Question for Topic 1

7. Of all the symptoms you have experienced because of Huntington's Disease, which do you consider to have the most significant impact on your daily life? **Please choose up to three symptoms.**

- a. Cognitive impairment (such as difficulty concentrating, difficulty with complex tasks)
- b. Chorea
- c. Fatigue
- d. Unsteady gait, difficulty walking
- e. Depression or Anxiety
- f. Slurred speech
- g. Weight Loss
- h. Difficulty swallowing
- i. Other symptoms not mentioned

Question for Topic 2

8. Have you ever used any of the following drug therapies to help reduce your symptoms of Huntington's disease? (Check all that apply)
- a. Tetrabenazine (Xenazine)
 - b. Antipsychotic drugs (such as **Risperdal, Haldol**)
 - c. **Antidepressants**
 - d. Other drug therapies not mentioned
 - e. I'm not sure
9. Besides your drug therapies, what other therapies have you used to help reduce your symptoms of Huntington's disease? (Check all that apply)
- a. Psychotherapy
 - b. Speech therapy
 - c. Physical therapy
 - d. Occupational therapy
 - e. Diet modifications
 - f. Behavioral therapy (such as counseling or support groups)
 - g. Other therapies not mentioned
 - h. I'm not using any other therapies

Appendix 4: Incorporating Patient Input into a Benefit-Risk Assessment Framework for Huntington's Disease

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 biologics³. 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 Huntington's Disease 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 Huntington's Disease below draws from various sources, including what was discussed at the Huntington's Disease Patient-Focused Drug Development meeting held on September 22, 2015. This sample framework contains the kind of information that we anticipate could be included in a framework completed for a drug under review for Huntington's Disease. 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>.

Dimensions	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<p>-Huntington’s Disease (HD) is a fatal genetic disorder that causes the progressive degeneration of nerve cells in the brain, leading to a wide range of symptoms. The most common symptoms are uncontrolled movements, cognitive impairments, emotional disturbances, slurred speech, and difficulty swallowing.</p> <p>- Each child of an HD parent has a 50% chance of inheriting the disease, and HD affects both genders equally. It is estimated that there are 30,000 symptomatic Americans living with HD, and over 200,000 individuals at risk of inheriting the disease⁴.</p> <p>-Typical onset of symptoms in adults occurs between ages 30 and 50. Juvenile HD is typically defined as beginning before age 20.</p> <p>-HD symptoms cause a significant detrimental effect on a patient’s quality of life, ability to perform any activities, and overall impact on societal engagement. As symptoms progress, patients become increasingly or fully dependent on others for care. Patients report living with anxiety, depression, fear of worsening symptoms, and fear of passing on the devastating disease to future generations.</p> <p><i>See the Voice of the Patient report for a more detailed narrative.</i></p>	<p>Huntington’s Disease is a hereditary, debilitating disease which has devastating impacts on patients and their families. There are many physical and emotional symptoms of the disease; however, many patients and caregivers report that the psychiatric symptoms are the most difficult to manage.</p>
Current Treatment Options	<p>-There is no cure for HD, and current treatments attempt to reduce the symptoms of HD. However, symptoms continue to worsen as HD progresses.</p> <p>-Xenazine (tetrabenazine) is indicated to treat the involuntary movements (chorea) of HD. Serious side effects include depression, suicidal thoughts, and suicidal actions.</p> <p>-Antipsychotics (such as haloperidol and risperidone) and antidepressants (such as citalopram or sertraline) are also frequently used to manage symptoms of HD.</p> <p>-Supportive care, such as occupational or physical therapy, to maximize physical function.</p> <p>-Other therapies include nutritional support, psychological counseling, family counseling, and speech therapy.</p> <p>-Patients also report that prayer, minimizing stress, dietary modifications, and exercise are a common part of their treatment regimen.</p> <p><i>- See the Voice of the Patient report for a more detailed narrative.</i></p>	<p>Treatment options for HD symptoms help to reduce the impact of symptoms. However, current treatment options do not adequately manage symptoms as they worsen.</p> <p>There is a continued need for additional effective and tolerable treatment options that can delay the onset of symptoms or greatly reduce the impact of symptoms for patients. These treatments are required to improve patients’ quality of life and daily functioning.</p>

⁴ Statistic from The Huntington’s Disease Society of America: <http://hdsa.org/what-is-hd/>