

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

Parkinson's Disease

Public Meeting: September 22, 2015

Report Date: April 2016¹

Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration (FDA)

¹ Report Update: May 2016

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Introduction

On September 22, 2015, FDA held a public meeting to hear perspectives from Parkinson's disease patients, caretakers and other patient representatives on the most significant effects of their disease, its impact on 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 between Fiscal Years 2013 - 2017, each focused on a specific disease area.

More information on this initiative can be found at

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>.

Overview of Parkinson's Disease

Parkinson's disease is a progressive and chronic neurodegenerative brain disorder that affects approximately 1 million people in the United States. Parkinson's disease affects both men and women; however, men are one and a half times more likely than women to have the disease. The condition is generally characterized by primary motor symptoms of resting tremor, bradykinesia, rigidity, and postural instability. Non-motor symptoms experienced by Parkinson's disease patients may include cognitive impairment, mood disorders, and sleep disturbances. The manifestation of motor and non-motor symptoms varies among patients. The progression of Parkinson's disease may differ markedly from patient to patient following diagnosis.

There is no cure for Parkinson's disease; therefore, the goals for treatment are to improve quality of life and manage the signs and symptoms of the disease. Several treatment options for Parkinson's disease are currently available and involve a wide range of administration routes including tablets, capsules, patches, subcutaneous injections, intramuscular injections and intrajejunal infusions. Carbidopa-levodopa remains the mainstay of treatment for the signs and symptoms of Parkinson's disease. Over the course of their disease, almost all patients with Parkinson's disease will take carbidopa-levodopa. In addition to carbidopa levodopa, other treatments include drugs such as dopamine agonists, COMT (catechol-O-methyltransferase) inhibitors, anticholinergics, and MAO-B (monoamine oxidase type B) inhibitors. Deep brain stimulation is also a potential therapeutic option for patients with advanced Parkinson's disease. Non-pharmacological management approaches include exercise, yoga, meditation, diet, and lifestyle modification.

Meeting overview

This meeting gave FDA the opportunity to hear directly from patients, caretakers, and other patient representatives about their experiences with Parkinson's disease and its treatments. Discussion focused on two key topics: (1) the effects of Parkinson's disease that matter most to patients, and (2) patients' perspectives on treatments for Parkinson's disease. The discussion questions (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. An FDA facilitator led the discussion, and a panel of FDA staff (Appendix 2) asked follow-up questions. Participants who joined the meeting via live

webcast (referred to in this report as web participants) were also able to contribute comments. In addition, 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 of how many participants shared a particular perspective on a given topic.

Approximately 45 Parkinson's disease patients and patient representatives attended the meeting in-person, and approximately 10 patients or patient representatives provided input through the live webcast. According to their responses to the polling questions, in-person and web participants represented an even distribution of gender. Most in-person participants were 61 years of age or older. A majority of meeting participants identified themselves as having received a Parkinson's disease diagnosis less than ten years ago. Although participants at this meeting may not fully represent the population of patients living with Parkinson's disease, FDA believes that the input reflects a range of experiences with its 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](#),² which was open until November 23, 2015. FDA received 29 comments to the public docket, the majority by individual patients. A few patient groups and healthcare providers also submitted surveys and patient group responses to the public docket.

More information, including the archived webcast 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 Parkinson's disease 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 Parkinson's disease that are not included in this report.

The input from the meeting and docket comments underscore the debilitating effect that Parkinson's disease has on patients' lives and the challenges patients face in finding therapy to manage the multiple challenges caused by their condition. Several key themes emerged from this meeting:

- Parkinson's disease is a progressive, devastating disease. Participants emphasized the difficulty of living with the unexpected onset and progression of symptoms. Many described living with daily motor symptoms which included bradykinesia, dyskinesia, tremor and dystonia. In addition to motor symptoms, participants also highlighted sleep disturbances, cognitive impairment, fatigue, and constipation.
- Parkinson's disease impacts all aspects of patients' lives. Participants described severe limitations in performing at work, caring for self and family, and maintaining relationships.

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.

Participants shared the emotional toll of living with social isolation and adjusting to significant lifestyle changes to manage their Parkinson's disease.

- The meeting reiterated the complexity of Parkinson's disease management. Participants described the burden of selecting the best available treatments to address their symptoms, the complexity of managing proper timing of medications in addition to pill burden (number and frequency of pills taken throughout the day), and the need for adjustment of their medication regimen because of unpredictable symptoms, changes in daily demands leading to increases in symptoms, as well as disease progression.
- Nearly all participants described using a combination of drug and non-drug treatments. Participants emphasized that the side effects of treatments were often as debilitating as the underlying disease symptoms. Many participants highlighted the benefits of incorporating non-drug therapies, such as exercise and diet modifications, with prescription regimens for optimal symptom management.
- Participants expressed the need for medications that were effective in delaying the onset of symptoms or slowing the progression of symptoms. Others focused on the progress of ongoing research and the potential for disease prevention (including stem cell research, determining predictive biomarkers, and clinical trial participation)

The patient input generated through this Patient-Focused Drug Development meeting and public docket comments strengthens FDA's understanding of the burden of Parkinson's disease on patients and the treatments currently used to manage Parkinson's disease and its symptoms. FDA staff will carefully consider this input as it fulfills its role in the drug development process, including 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 directly support our benefit-risk assessments for products under review. This input may also be of value to the drug development process more broadly. In addition, the report may be useful to drug developers as they explore potential areas of unmet need for Parkinson's disease patients such as limiting disease progression or increasing symptom control. It could also point to the potential need for development and qualification of new outcome measures in clinical trials.

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

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

Five panelists (Appendix 2) provided comments to start the dialogue, including two women and three men. The panelists provided a range of experiences with Parkinson's disease: two panelists spoke of experiencing symptoms for several years prior to diagnosis, two panelists described living with Parkinson's disease for over twenty-five years, and one panelist shared her late mother's experiences with Parkinson's disease progression. Panelists described living with the symptoms of Parkinson's disease and its impact on daily life with compelling detail. During the large-group facilitated discussion, participants indicated by show of hands that their experiences were reflected in the panelists' comments.

Perspectives on most significant symptoms

In polling question (Appendix 3, Q6) patients were asked to identify up to three symptoms that have the greatest impact on daily life. Motor symptoms, impaired balance and coordination, cognitive impairment, and sleep disturbances received the highest number of responses. Responding web participants reported similar symptoms to those participating in person. The facilitated discussion provided a detailed view into how these symptoms manifest. Throughout the discussion, participants commented on the unpredictability of their Parkinson's disease symptoms, and many shared their experiences on how symptoms have progressed.

Motor Symptoms

The most frequently identified symptoms by in-person and web participants were motor symptoms. Meeting participants described the manifestation of motor symptoms using a wide range of terms such as bradykinesia, dyskinesia, and dystonia. One participant expressed his bradykinesia as, "not just a physical change in movement, velocity, but a pervasive slowing of thought patterns, like a freezing of synapses." One panelist described her dyskinesia is so severe that "it looks like I'm having a seizure, and very painful." A participant expressed that during a moment of dystonia "my entire body goes stiff...my mouth is often forced open in a painful position, or my mouth is forced closed with my tongue stuck out." The additional examples from participants help to put these symptoms in the context of daily life:

- "I was having difficulty... controlling my forward motion. I was carrying one end of a cabinet to install and could not stop [moving forward]."
- "[Dystonia] was so debilitating that it became difficult for me to walk more than several blocks before I had to stop to let the [foot] cramps ease up."
- "I had terrible dyskinesia....I would knock over all the glasses at the table [while eating]."
- "I was unable to type or use a computer mouse with my right hand, and unable to use my right foot and leg to drive [following diagnosis]."

Participants also shared experiencing "freezing." One participant described freezing as "the sudden inability to move my legs, as if they were set in blocks of hardened concrete." Another participant described it as "the sensation of suddenly becoming stuck to the floor and temporarily unable to walk." In addition, participants discussed experiencing tremors, festination, shuffling gait, rigidity, limping and hand flutter due to Parkinson's disease.

Participants also described how their motor symptoms deteriorated over time. One caregiver shared that over a period of 3 years, her mother's Parkinson's disease progressed from stiffness to being fully wheelchair bound. One participant echoed this comment sharing, "Since my diagnosis nine years ago, difficulty moving has increased exponentially and now includes problems walking, eating, showering, turning over in and getting out of bed." Participants noted experiencing impaired balance and coordination due to motor symptoms as "the most challenging of all." Participants expressed that balance issues often led to falling and fear of falling. One participant shared that the fear of falling "is always in the back of my mind."

Several panelists stated that stress exacerbated their motor symptoms and impaired balance; this comment resonated with several in person participants. Participants' also identified additional triggers

that worsened their motor symptoms including: lack of sleep, anxiety, large crowds, stress, temperature change, and the feeling of being rushed to complete a task.

Cognitive Impairment

Several participants highlighted the cognitive effects of Parkinson's disease on their day to day activities. For some participants, cognitive impairment was manifested as being unable to remember words, particular periods of time and people. Participants shared specific instances:

- "If you asked me, I wouldn't [be able to] tell you what I had for breakfast. I forget things and it is very disruptive to a normal life."
- "I can't recall names or places or proper nouns."
- "I'm now at the point [in my disease progression] that I'm having difficulty remembering words. I have lots of cognitive problems."
- "It would take [my mother] some time to realize where she is and who she is... [at times] she doesn't know who I am."

Some participants characterized their cognitive impairment as inability to focus on or complete a task in the manner that they desired in vivid detail in the statements below:

- "I have difficulty understanding simple questions, and it feels like I'm in a fog."
- "I often go from task to task without ever actually completing anything."
- "If it's a 10-step task [my husband] get[s] lost in about 2 or 3...and then never complete[s] the task."

One caregiver shared her late mother's communication issues due to cognitive difficulties. "As her disease progressed, she would answer us in Japanese, which we do not speak. She sometimes started her sentence in Korean and ended in English." One participant highlighted the frustration with cognitive impairment stating, "People think you're doing it on purpose...they don't understand it's actually a symptom of the disease that's preventing you [from thinking]."

Sleep Disturbances

Over one-third of meeting participants identified sleep disturbances as one of their most significant symptoms. A wide range of sleep disturbances were reported, including difficulties falling asleep and staying asleep. Participants described their sleep patterns as "chaotic" and "not restorative." One participant shared that he was unable to get refreshing sleep due to, "screaming in the night and awakening at all hours." Participants also commented that lack of sleep amplified other Parkinson's disease symptoms. One woman shared that lack of sleep caused her "right arm to tremor all night." Another participant linked his lack of sleep to impaired thinking and slow reaction time. Participants also mentioned that sleep disturbances sometimes lead to fatigue symptoms which may persist into the next day. One participant shared that he had not had restorative sleep for many years. Comments regarding fatigue resonated with meeting participants.

Other symptoms

Participants described a number of other symptoms that have a significant impact on their daily lives.

- Several participants identified **constipation** as a significant symptom. One woman stated, “Using the restroom is difficult...because my stomach muscles are often too cramped.” One participant commented on living with “constant” and “chronic” constipation that causes her to be homebound for several days each week. Some participants expressed the need for constant monitoring of their diet due to constipation. One participant shared, “I have to really watch meat...it will take me several days to digest and cause constipation.”
- A few participants experienced **orthostatic hypertension** resulting from, “standing still for a while” or after “[getting] up very quickly from a lying-down position or sitting.” One participant also shared that she “[does not] stand still when it’s hot outside” because it worsened her orthostatic hypertension.
- A few participants noted **micrographia** as a bothersome symptom. This progressively smaller handwriting pattern was described as an “annoyance.” One participant noted that his handwriting “would start out relatively normal, but by sentence end...was illegible scrawl.”
- Several participants commented that they experienced significant **depression and anxiety**, especially as their disease progressed. One participant commented that her anxiety occurred whenever she needed to “complete a particular task.” A caregiver explained that when her mother could no longer walk or move, “she felt powerless” and became depressed. Another participant mentioned experiencing “episodes of tearful weeping.”
- Other symptoms noted by participants included loss of smell, weight loss, dyspnea, restless leg, difficulty swallowing, pain, sweating, muscle aches, and speech issues.

Overall impact of Parkinson’s disease on daily life

Throughout the meeting, participants described the physical and social impact that living with Parkinson’s disease has had on their lives. Many also highlighted the emotional burden of living with Parkinson’s disease, sharing that their condition felt “frustrating” and “incredibly scary.” As one participant summarized, “Since my diagnosis, nothing has been normal or predictable.” Other perspectives on living with Parkinson’s disease are shared below:

- **Reliance on others.** Participants shared their perspectives on relying on caregivers. Several participants highlighted the effect of this reliance upon how they care for and are perceived by their family. One participant noted that family members sometimes become frustrated with his lack of ability to complete a task. He shared his family’s sentiments: “Better not give him that assignment if you want it done before the end of the day.” Several participants expressed reliance on caregivers for a range of daily activities due to problems walking, eating, showering, and standing. The following examples illustrate the experiences shared in the discussion of this impact:
 - “I’m supposed to be the caregiver of my children...they’re only teenagers, and they’re beginning to help.”

- “It worries me to contribute less and less to my family’s care and not be able to always help.”
- “I fear the people I love most in the world will have to take care of me.”
- “He inadvertently injures our children when trying to help put on shoes or clothes...[due to] inability to control his muscles.”
- **Ability to perform at work.** Participants shared that their symptoms, particularly motor symptoms, impaired balance, and cognitive impairment, had significant impacts on their ability to perform at their job. One participant shared an experience of quitting a position due to impaired balance, stating, “the responsibility [of the position]...it was just haunting me and causing me to fall down.” Other participants noted that they could no longer continue their chosen career paths due to cognitive difficulties and an inability to control motor symptoms.
- **Isolation and impact on relationships.** Many participants commented that the lack of energy, anxiety, and motor symptoms led to social isolation. One participant shared that she had increased anxiety when making social plans, saying, “, I often cancel at the last minute because I get so anxious going out... because of this, I find myself confined to the house on many days.” Another participant shared, “I’ve lost friend who just couldn’t get their arms around this illness.” Participants expressed that their Parkinson’s disease symptoms often led to negative perceptions in public environments. Some participants shared instances of being characterized as lazy or “looking a little slow.” A few described being mistakenly perceived as drunk due to uncontrollable motor symptoms or the inability to complete tasks.

Topic 2: Patient Perspectives on Treatments for Parkinson’s disease

The second discussion topic focused on patients’ experiences with therapies used to address their Parkinson’s disease symptoms. Five panelists, including four men and one woman, provided comments to start the dialogue. Two men discussed the hardships of pursuing treatment due to lack of timely diagnosis, one man shared detailed experiences with deep-brain stimulation, another man stressed the importance of seeking healthcare professionals which specialize in Parkinson’s disease management and one woman highlighted the importance of emerging research in stem cells and regenerative medicine. Panelists shared their experiences with complex regimens which included a variety of prescription treatments, alternative therapies, and lifestyle changes. Panelists stressed their desire for more effective treatment options.

In the large-group facilitated discussion that followed, experiences voiced by participants reflected those shared by panelists. Participants identified the importance of a personalized treatment regimen incorporating experiences of supplement and vitamin use, prescription drugs and lifestyle modifications in efforts to manage symptoms. Participants described in detail the benefits and downsides of their current treatment regimens. Participants also shared their considerations for what an ideal treatment for Parkinson’s disease would be.

Prescriptions and over-the-counter drugs

According to a polling question (Appendix 3, Q7), the majority of in-person and web participants reported experiences taking carbidopa-levodopa formulations, dopamine agonists, and other drug therapies. Prescription drug therapies were described as having widely varying degrees of effectiveness,

and many participants noted limited or decreased benefit over time because of Parkinson's disease progression and harmful side effects.

Carbidopa-Levodopa

Carbidopa-levodopa (including Rytary, Duopa, Sinemet and Sinemet CR) was the most frequently mentioned Parkinson's disease treatment. Many participants expressed specific improvements in managing tremor, balance, gait, and overall mobility with carbidopa-levodopa. Some participants described carbidopa-levodopa as a "miracle drug" which showed significant improvement in their condition. One participant shared that taking Sinemet with amantadine greatly improved his dyskinesia.

Several participants commented that they had to increase the formulation strength or dosing frequency of Sinemet as their symptoms worsened. One woman shared that the dosage of her original regimen of carbidopa-levodopa nearly doubled over the course of five years. One web participant described that changed formulations from Sinemet to Sinemet CR to meet increasing dosage demands.

Several participants commented that despite the benefits of carbidopa-levodopa, they experienced significant down-sides. Most participants identified developing severe dyskinesia, which "became more of a problem than the actual symptom [the medication] was treating." One participant described experiencing dyskinesia which "would last for two exhausting hours." Some participants stated that they often questioned whether to continue treatment because of the severity of dyskinesia.

FDA asked participants to comment on specific experiences with other formulations of carbidopa-levodopa, including Duopa and Rytary. One woman shared, "[Rytary] didn't work for me at all. And it caused me to be angry all the time." Other participants expressed that it was difficult to determine the correct dosage needed for symptom improvement with Rytary, and that they often experienced severe dyskinesia as a side effect. Meeting participants acknowledged familiarity with the Duopa formulation; however, there were no comments provided on experiences using it. One caregiver shared that the lack of experience with new formulations may be due to, "debating the pros and cons of each medication and the hesitation to change something that seems to be working."

Dopamine Agonists

Over half of participants shared experiences taking dopamine agonists, most commonly, Requip (ropinirole) and Mirapex (pramipexole), for movement and balance improvement. One participant stated, "ropinirole has been very helpful for restless leg syndrome at bedtime." One web participant shared positive experiences with Mirapex extended-release (ER) formulation, stating "Mirapex has helped a lot [with my symptoms]. I went from four Mirapex [tablets] a day down to one Mirapex[tablet] daily when I switched to ER (extended-release)."

Participants also discussed side effects associated with their use of dopamine agonists. Some participants discontinued Mirapex due to "sleep attacks," which were described as moments when "[your] conscious mind is switched off and [you] sort of go blind." One participant shared an instance of a sleep attack which caused him to drop his laptop unexpectedly. Another participant said that she experienced orthostatic hypotension whenever she missed a Mirapex dose. Participants also described experiences of impulsive behavior and feet swelling as reason for reducing Mirapex use.

A few participants shared experiences using additional dopamine agonists, Apokyn (apomorphine) and Neupro (rotigotine), to manage unexpected motor symptoms. One participant expressed difficulty with patch adherence of Neupro. Another participant shared an experience of using apomorphine to control unexpected symptoms in the work place.

Additional treatments

Participants also briefly mentioned the use of additional therapies to address their Parkinson's disease symptoms. These therapies included: monoamine oxidase inhibitors (MAOI's) to address motor symptoms, Ambien (zolpidem), Provigil (modafinil), and melatonin to address sleep issues, and Amitiza (lubiprostone) and over the counter laxatives to address constipation symptoms and pain medications.

Medical Procedures

Meeting participants also discussed their experiences with deep brain stimulation (DBS), a surgical procedure used to reduce involuntary motor symptoms. Many participants described experiencing a significant improvement in dyskinesia after undergoing DBS surgery. One participant shared that following deep brain stimulation surgery he was "disease-free from a motor standpoint." However, participants shared that DBS did not address all symptoms, including: increased frequency of off time, loss of smell, and cognitive issues. A woman expressed discomfort following the procedure and stated, "the battery [for DBS], it's quite painful in my chest at times. One participant shared his experience of using an assistive device to address the "head-drop" he has experienced with Parkinson's disease. He shared that "without this [device] my chin would be on my chest" and also noted additional discomfort with use of the device.

Non-drug therapies

Nearly all meeting participants commented on the importance of a holistic approach to managing their Parkinson's disease symptoms. Participants shared that exercise specifically improved sleep, cognitive function, mood and motor symptoms. One participant stated, "exercise is more important than the pills we take." A few participants expressed the importance of targeted workouts, including one participant who said, "when I am doing a legs workout, I feel the difference in my body." Exercise regimens included intense interval training programs, rowing, cycling, hiking, dancing, walking several miles every day, Tai Chi, Qigong, and yoga.

The majority of meeting participants identified the importance of diet and nutrition modifications. Participants stressed throughout the meeting the positive effects of eating healthy foods as well as avoiding meat products to improve digestion and medication effects. In addition to diet changes, a few participants also reported vitamin and supplement use. Participants described mixed results with the use of vitamins and supplements.

Treatment downsides

In addition to the medication side effects aforementioned, participants also described broader treatment downsides they experience while managing Parkinson's disease.

- Many participants described the significant impact of **pill burden** on their daily lives; one participant shared that this was the "hardest challenge" of Parkinson's disease treatments. One participant mentioned taking 14 medications throughout the day and 15 pills at nighttime. Some participants discussed the large amount of planning involved in balancing food intake,

medication use and daily needs. Another participant described the task of balancing medication and food as tedious in nature and requiring a lot of focus.

- Participants expressed frustration with periods of “off-time,” which was described as unpredictable exacerbation of symptoms during which medications were less effective. A few described the unpredictability that off-time brought into their lives on a daily basis. One participant shared, “[symptoms] can vary not only from day to day, but from hour to hour.” This comment resonated with many participants. One participant stated, “the various off-and-on states, is what makes this disease so hard to live with.” Another participant described experiencing “several months of good on-time, and then off-time where I can’t even stabilize myself with a walker.”
- Participants expressed frustration regarding limited access to treatment options, specifically related to insurance coverage of medications that were used off-label.

Perspectives on an ideal treatment for Parkinson’s disease

Participants provided feedback on what they would look for in an ideal treatment for Parkinson’s disease. Some participants stated that an ideal treatment would minimize dosage and administration burden, and have minimal side effects. For example, one participant expressed, “the perfect treatment would be a once-a-day pill, patch or inhalant that controls all symptoms, minus side effects and without on-off times.” This sentiment resonated with many participants.

Participants also expressed the desire for holistic treatment approaches incorporating both drug and non-drug therapies. One participant described his ideal treatment plan as “three days of disciplined, intense exercise; one day of exercise alternatives, such as cycling, hiking, or dance; two days of Tai Chi; and a little medication to round it off.”

Throughout the meeting, participants raised a number of other considerations that they believed were important relating to Parkinson’s disease treatment and drug development more broadly, including the progress of stem cell research, clinical trials for new surrogate markers, and the need for a greater focus of disease prevention in addition to treatment. Many participants commented on the need for increased awareness and education to properly diagnose and treat Parkinson’s disease. Participants also commented on the importance of early diagnosis for improvement of quality of life.

Summary of Comments Submitted to the Public Docket

FDA received 29 comments to the public docket that supplemented input gathered during the Patient Focused Drug Development meeting on Parkinson’s disease . The majority of comments were submitted by Parkinson’s disease patients and caregivers. Several healthcare professionals submitted comments that collated input from multiple patients or that otherwise reflected their personal experience treating Parkinson’s disease patients. Three surveys were submitted by advocacy organizations: Parkinson’s Action Network, 23andMe, and PatientsLikeMe.³ These surveys examined patients’ and caregivers’

³ Survey comments may be viewed within the Federal Register Public Docket Comments <https://federalregister.gov/a/2015-17556> . FDA has not conducted a thorough review of the design, conduct or analysis of these surveys. This report may reference select survey results, which should be considered illustrative of results which either reiterated or expanded upon input from the September 22, 2015 meeting.

perspectives on their most significant symptoms, the impact of Parkinson's disease on quality of life, and treatment options. The submitted surveys varied in survey type, participant demographics, and sample size.

The docket comments reflected the experiences and perspectives shared at the meeting on the symptoms that affect their lives the most, the impacts of their disease on daily life, and their experiences with treatments for Parkinson's disease. The following is a brief summary of comments provided with particular focus placed on experiences or perspectives that were not addressed or raised in detail during the meeting.

Submitted comments on symptoms of Parkinson's Disease

Comments submitted to the public docket reiterated the burdensome nature of Parkinson's disease. The symptoms of Parkinson's disease mentioned in the docket were similar those discussed during the meeting. The most commonly mentioned symptoms included: motor symptoms, cognitive impairments, sleep issues, and speech issues. These symptoms were also echoed throughout multiple survey results submitted to the docket.

Commenters echoed input from meeting participants on the impact of motor symptoms. Commenters expressed tremor as a burdensome side effect describing it as "constant" and "violent." In addition commenters reiterated a variety of motor symptoms including rigidity, jerking, cramping, and muscle stiffness. A few commenters mentioned that their motor symptoms have worsened over time.

Other commenters reemphasized cognitive issues such as memory loss, executive dysfunction, and difficulties concentrating frequently throughout the docket. One woman described her memory impairment as "frustrating and embarrassing." One caregiver described the difficulty for her husband to "start and finish a task without losing his place during the task."

A few emphasized speech issues. Commenters mentioned experiencing stuttering, hesitancy with speech, and noticeable shifts in the volume of their voice while speaking. One commenter noted, "It is embarrassing, and I hesitate to try to talk."

Other symptoms mentioned included constipation, impaired balance, difficulty swallowing, orthostatic hypertension, anxiety, and loss of smell. The findings of the submitted surveys were also consistent with input received during the meeting. Commenters also noted that symptoms "come and go"; often fluctuating throughout the day.

Similar to the input from meeting participants, commenters also emphasized stress and cold weather as factors that worsen their Parkinson's disease symptoms. Triggers were also addressed through the submitted surveys. For example, mental distress (which included feeling of stress, anxiety, intense emotions, and fear of the public), fatigue, sleep, and physical health were the most commonly reported triggers identified in the PatientsLikeMe survey. Respondents of the Parkinson's Action Network and 23andMe surveys also reiterated the effect of stress upon Parkinson's disease symptoms.

Submitted comments on the overall impact of Parkinson's disease on daily life

The docket comments reiterated the burden that Parkinson's disease and its symptoms have on daily life, such as the lack of ability to perform activities and the reliance on others for care. Many described how driving, working, household chores, and other day to day task were a struggle due to Parkinson's

disease. One commenter shared, “almost all extracurricular activities such as sports and traveling have come to a complete stop.” Commenters expressed the fear and emotional burden of relying on others to assist with daily needs. One commenter expressed, “I worry about the loss of my independence, the potential inability to drive a car, and the possible dependence on a caregiver to dress and feed me.”

Several commenters also expressed isolation and impact on relationships they have experienced due to Parkinson’s disease. One commenter linked experiences of fatigue as contributors to her isolation and inability to gather with friends. Commenters also reiterated the negative perception of Parkinson’s disease patients by family members or public. Some commenters shared experiences of people assuming they are drunk and/or mentally handicapped. One commenter also expressed that he sometimes felt that he was being “treated as a child” due to his Parkinson’s disease symptoms.

Submitted comments on current treatments for Parkinson’s disease

The submitted comments reflected the challenges of managing the many symptoms of Parkinson’s disease, while making difficult decisions about treatments. The range of commenters’ experiences was similar to that expressed by meeting participants. Carbidopa-levodopa formulations (including Sinemet, Rytary and Duopa) were most frequently mentioned by docket commenters and survey respondents of the submitted surveys. Other drug classes (e.g., MAOIs) identified at the meeting were also frequently mentioned, in addition to a number of therapies or medical procedures that were not mentioned at the meeting (e.g., muscle relaxants reported by respondents to the 23andMe survey).

The discussion on prescription therapies was similar to input received at the public meeting. Docket commenters highlighted coping with fluctuation in symptom relief and the need to balance desired treatment efficacy while experiencing burdensome side effects. For example, one commenter stated that with every year of Sinemet use, the drug becomes “less effective than the year before.” Another commenter described slowly reducing his use of carbidopa-levodopa due to the side effects he experienced. One caregiver shared that her mother had to discontinue use of Rytary (“due to delusional effects”) and later, the Duopa pump (“due to pump use complications”). Survey results also reiterated treatment downsides of experiencing “off-time,” mentioned in-person during the meeting. The survey also reported the most common treatment complaint by participants to be “wearing off/ need for frequent dosing.” Commenters also reiterated the pill burden associated with their prescription medication regimen. As one stated, “Timing of medications requires planning at all times.”

In addition to carbidopa-levodopa formulations, commenters and survey respondents also shared experiences of using drug classes such as MAOIs, dopamine agonist, sleep aids, and laxatives similar to in-person meeting participants.

Non-drug therapies were also frequently mentioned, including diet modifications, vitamin use, and exercise. Commenters reiterated the importance of a holistic approach and described the impact of diet, vitamins, and exercise use. Commenters expressed positive experiences with the use of calcium, potassium, and magnesium to manage muscle cramps. Commenters also expressed using changes in diet to address constipation. Commenters echoed the importance of exercise and mentioned various exercise regimens included biking, swimming, and dancing. Survey respondents also echoed this result, indicating that exercise improved symptoms (PatientsLikeMe result) and that patients relied on exercise for appropriate symptom management (Parkinson’s Action Network result).

A few commenters expressed their experiences with the deep brain stimulation (DBS) surgical procedure. Commenters reiterated the positive effects of DBS in symptoms management and slowing

disease progression. One commenter stated, “My DBS stops my tremor so I can do everything as I could before.” Similar to the meeting participants, commenters did express that some symptoms of dystonia and cognitive function still remain unaddressed by DBS similar to meeting participants. One commenter expressed concerns regarding the risks posed by his DBS device, specifically related to electromagnetic interference (with other medical devices, airplanes). Another commenter shared that due to a complication of DBS he has lost the ability to speak.

Submitted comments on ideal treatments for Parkinson’s disease

Several perspectives were provided on ideal treatments for Parkinson’s disease. The top three aspects of ideal treatment desired by commenters included medications with less “off” time, better symptom control, and less side effects. These comments were reinforced by survey responses. Other aspects of treatment mentioned included affordability, increased knowledge in the medical and research community, in addition to holistic treatment approaches.

Conclusion

The Patient Focused Drug Development meeting on Parkinson’s disease provided FDA an important opportunity to obtain patients’ in-depth point of view on the severity of Parkinson’s disease, its impact on daily life, and available treatment options. Parkinson’s disease is a progressive, debilitating disease that severely impacts a patients day-to-day functioning and has a devastating impact on their lives and the lives of their caretakers. Participants described losing their physical function, the ability to care for themselves, and to participate in activities. The insight provided during this meeting will aid in FDA’s understanding of what patients truly value in a treatment and inform the agency’s evaluation of the benefits and risk of future treatments for Parkinson’s disease patients.

We greatly appreciate the openness of participants, who were able to share candidly their experiences with Parkinson’s disease and their various approaches to treatment management. FDA shares the patient community’s desire and commitment to furthering the development of additional safe and effective drug therapies.

Appendix 1: Meeting Agenda and Discussion Questions



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



September 22, 2015

12:30 – 1:30 pm	Registration
1:30 – 1:35 pm	Welcome Soujanya S. Giambone, MBA <i>Office of Strategic Programs (OSP), Center for Drug Evaluation and Research (CDER), FDA</i>
1:35 – 1:40 pm	Opening Remarks Billy Dunn, MD <i>Director, Division of Neurology Products (DNP), Office of New Drugs (OND), CDER, FDA</i>
1:40 – 1:50 pm	Overview of FDA's Patient-Focused Drug Development Initiative Theresa Mullin, PhD <i>Director, OSP, CDER, FDA</i>
1:50 – 2:00 pm	Background on Disease Area and Treatment Susanne Goldstein, MD <i>Medical officer, DNP, CDER, FDA</i>
2:00 – 2:05 pm	Overview of Discussion Format Soujanya S. Giambone, MBA <i>OSP, CDER, FDA</i>
2:05 – 2:35 pm	Panel #1 Comments on Topic 1 Topic 1: Disease symptoms and daily impacts that matter most to patients. A panel of patients and patient representatives will provide comments to start the discussion.
2:35 – 3:10 pm	Large-Group Facilitated Discussion on Topic 1 Patients and patient representatives in the audience are invited to add to the dialogue.
3:10 – 3:20 pm	Break
3:20 – 3:50 pm	Panel #2 Comments on Topic 2 Topic 2: Patient perspectives on current approaches to treating Parkinson's Disease. A panel of patients and patient representatives will provide comments to start the discussion.
3:50 – 4:25 pm	Large-Group Facilitated Discussion on Topic 2 Patients and patient representatives in the audience are invited to add to the dialogue.

4:25 – 4:55 pm

Open Public Comment

4:55 – 5:00 pm

Closing Remarks

Eric Bastings, MD

Deputy Director, DNP, OND, CDER, FDA

Discussion Questions

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

1. Of all the symptoms that you experience because of your condition, which **1-3 symptoms** have the most significant impact on your life? (Examples may include difficulty moving, pain, constipation, difficulty concentrating or remembering, daytime sleepiness 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 daily hygiene, feeding, dressing, etc.)
 - a) How do your symptoms affect your daily life on the **best days**? On the **worst days**?
3. How has your ability to cope with symptoms **changed over time**?
 - a) Do your symptoms come and go? If so, do you know of anything that makes your symptoms better? Worse?
4. What **worries you most** about your condition?
5. Are there friends or family that you can no longer visit because of your illness?

Topic 2: Patients' perspectives on current approaches to treating Parkinson'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 (for example; depression, constipation, memory difficulty, sleepiness)?
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?
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, , need to visit your doctor or take medications frequently cause sleepiness, etc.)
4. Assuming there is no complete cure for your condition, what specific things would you look for in an **ideal treatment** for your condition?

Appendix 2: FDA and Patient Panel Participants

FDA Panelist

Ellis Unger, Office of Drug Evaluation, CDER

Billy Dunn, Division of Neurological Products, CDER

Eric Bastings, Division of Neurological Products, CDER

Susanne Goldstein, Division of Neurological Products, CDER

Kenneth Bergmann, Division of Neurological Products, CDER

Leonard Kapcala, Division of Neurological Products, CDER

Gerald Podskalny, Division of Neurological Products, CDER

Theresa Mullin, Office of Strategic Programs, CDER

Peter Como, Division of Neurological and Physical Medicine Devices, CDRH

Lei Xu, Division of Clinical Evaluation and Pharmacology/Toxicology, CBER

Patient Panelists

Topic 1

Daniel Lewis – Patient

Karl Robb – Patient

Todd Hebb - Patient

Rosa Kim - Caregiver

Rebecca Houde - Patient

Topic 2

Bill Patterson- Patient

Steven Dewitte- Patient

Gary Rafaloff- Patient

Jennifer Raub- Patient

Kevin Kwok – Patient

Appendix 3: Meeting Polling Questions

1. Where do you live?
 - a. Within Washington, D.C. metropolitan area (including the Virginia and Maryland suburbs)
 - b. Outside of the Washington, D.C. metropolitan area

2. Have you ever been diagnosed as having Parkinson's Disease?
 - a. Yes
 - b. No

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

4. Age:
 - a. Younger than 30
 - b. 30-40
 - c. 40-50
 - d. 50-60
 - e. 60-70
 - f. 71 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

6. Of all the symptoms you have experienced because of Parkinson's Disease, which do you consider to have the most significant impact on your daily life? **Please choose up to three symptoms.**
 - a. Motor symptoms (slowed movement, tremor)
 - b. Impaired balance and coordination
 - c. Constipation
 - d. Sleep issues (such as falling asleep, staying asleep or abnormal dreams)
 - e. Cognitive impairment (such as difficulty concentrating, difficulty with complex tasks)
 - f. Fatigue and loss of energy
 - g. Difficulty swallowing/drooling
 - h. Depression or anxiety
 - i. Other symptoms not mentioned

7. Have you ever used any of the following drug therapies to help reduce your symptoms of Parkinson's Disease? (check all that apply)
- a. Carbidopa-levodopa (such as Duopa, Sinemet, Rytari Stalevo)
 - b. Dopamine agonists (such as Parlodel, Mirapex, Requip)
 - c. Monoamine oxidase B (MAO-B) inhibitors (such as Eldepryl, Azilect, Zelapar)
 - d. Catechol-O-methyltransferase (COMT) inhibitors (such as Comtan, Stalevo, Tasmar)
 - e. Anticholinergics (such as Artane, Cogentin)
 - f. Amantadine (Symmetrel)
 - g. Deep brain stimulation (DBS)
 - h. Drug therapy to treat hallucinations, depression and/or anxiety
 - i. Other drug therapies not mentioned
8. Besides your drug therapies, what therapies have you used to help reduce your symptoms of Parkinson's Disease? (Check all that apply)
- a. Exercise
 - b. Diet and nutrition modifications
 - c. Counseling and support groups
 - d. Physical Therapy
 - e. Alternative therapies (such as massage, yoga, acupuncture)
 - f. Other therapies not mentioned
 - g. I'm not using any additional therapies

Appendix 4: Incorporating Patient Input into a Benefit-Risk Assessment Framework for Parkinson'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 biologics⁴. 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 Parkinson'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 Parkinson's disease below draws from various sources, including what was discussed at the Parkinson'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 Parkinson'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.

⁴ Commitments in the fifth authorization of the Prescription Drug User Fee Act (Parkinson's disease UFA V) include further development and implementation of the Framework into FDA's review process. Section 905 of the FDA Safety and Innovation Act also requires FDA to implement a structured benefit-risk framework in the new drug approval process. For more information on FDA's benefit-risk efforts, refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>.

Sample Parkinson's disease Benefit-Risk Assessment Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> – Parkinson's disease is a debilitating, incurable disease that damages the nerve cells that produce the chemical messenger dopamine. – Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease. The prevalence of Parkinson's disease is 0.5 - 1% among persons age 65 to 69; 1-3% among persons 80+ years of age. – Core motor symptoms include bradykinesia (a decrease in spontaneity and movement), rigidity, tremor, and postural instability. – Other symptoms may include depression and other emotional changes; difficulty in swallowing, chewing, and speaking; urinary problems or constipation; skin problems; and sleep disruptions. – Motor fluctuations, especially periods of "Off" time and "On" time with troublesome dyskinesia (involuntary movements), put the patient at an increased risk of comorbid complications 	<p>Parkinson's disease is a progressive, serious disease which takes a large physical and emotional toll on patients. Over time it can significantly impact a patient's quality of life and place a large burden on patients' ability to live independently and functionally perform daily task without assistance.</p>
Current Treatment Options	<ul style="list-style-type: none"> – There is no cure for Parkinson's disease; however, there are a number of FDA approved treatments to manage symptoms of Parkinson's disease. – Pharmacologic treatment options for Parkinson's disease include the following: carbidopa-levodopa formulation, dopamine agonist, catechol-O-methyltransferase (COMT) inhibitors, monoamine oxidase inhibitors-B inhibitors (MAOI), anticholinergics, amantadine, and neuroleptic drugs. – Other treatments sometimes used to treat cope with emotional aspects of Parkinson's disease include antidepressants/anxiolytics. – Deep brain stimulation (DBS) is a potential therapeutic option for advanced Parkinson's disease. DBS may result in significant benefit. Downsides include neuropsychiatric adverse effects and limited effectiveness. Thus, many patients are unable or reluctant to undergo DBS. – Patients also pursue a holistic approach to treatment, which include exercise and dietary supplementation. 	<p>Drug treatments are available; however, efficacy varies from patient to patient and may also be accompanied by side effects which may limit benefits or preclude use of these medications. Additionally, frequency of dosing and route of administration can often be burdensome on patients. Thus, there is continued need additional, tolerable and effective treatment options.</p>