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Expert Testimony at the Food and Drug Administration: Who Wants the Truth?

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Abstract

I participated as an invited guest speaker at a Food and Drug Administration Advisory Panel meeting to provide expert background information on the potential clinical utility of dopaminergic neurons in the human brain. My conclusion at the end of the talk was that currently no clinical applications were justified. The purpose of the panel meeting was to advise the FDA regarding potential approval of a new drug application for a radiopharmaceutical that can be used to image dopaminergic pathways in the brain of living humans. After giving my presentation, I was permitted to observe the FDA and Pharma presentations but not permitted to ask or answer questions. This raises concerns about whether the FDA panel obtains a fair and unbiased review of the relevant data.

Keywords

FDA; conflict of interest; expert testimony; neuroimaging; Parkinson disease

In this article, I describe my rather surprising experience as a guest speaker at a Food and Drug Administration (FDA) Advisory Committee meeting. It all began on June 11, 2009 when an email invitation arrived from the Division of Medical Imaging and Hematology Products at the Food and Drug Administration (FDA) requesting that I participate as a guest speaker at the August 11, 2009 meeting of the Peripheral and Central Nervous System Advisory Committee. At that meeting, according to the email, “the Committee will discuss a new imaging agent to be used in the assessment of dopaminergic neuron function,” and I was asked “to speak on the topic of differential diagnosis of patients with movement disorders and the role of neuroimaging in the evaluation of these patients.” I have more than enough work to do, but this sounded like an intriguing opportunity. After all, I have more than 25 years experience with neuroimaging research in Parkinson disease and related conditions with particular expertise in imaging dopaminergic pathways in the brain. I have had multiple grants from the National Institutes of Health supporting my neuroimaging research. One of these grants entitled “Validation of Neuroimaging Biomarkers of Nigrostriatal Neurons” is precisely designed to develop and validate neuroimaging

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biomarkers of dopaminergic pathways – which include nigrostriatal neurons – a major component of dopaminergic pathways. Of course, it may be relevant to disclose that I originally proposed this grant since I was rather concerned that multiple national and international studies had applied neuroimaging measures of dopaminergic pathways as endpoints of clinical research studies without having, at least in my mind, adequate validation of the methods (Ravina et al., 2005). I have been a rather hard-nosed person with regard to what constitutes adequate validation. The other part of my background that is relevant to disclose is that I am Head of the Movement Disorders Center at Washington University in St. Louis. In that role, I am responsible for a large clinical, teaching and research operation that focuses on Parkinson and related disease. I have always been a rather serious clinical-educator constantly grilling medical students, neurology residents and movement disorders fellows on how any test that they order for a patient helps with decision-making for that patient. “If the test results will not alter decision making then do not order it” many trainees have heard me emphasize. Given this background and my Missouri upbringing (the Show Me state), I thought it was reasonable to respond affirmatively to this invitation. After all, this would be my chance to provide a non-industry perspective and clearly state my position on the topic at hand. And, my position was clear – I do not believe that current evidence justifies the clinical application of molecular neuroimaging of dopaminergic systems in the brain.

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Let me first give you some background on the potential clinical relevance of measuring dopaminergic pathways in the brain. Abnormalities of dopaminergic pathways in the brain underlie several neurologic and psychiatric illnesses and may also be critically important to treatment of those conditions. The most straightforward example is idiopathic Parkinson disease, a disease that primarily affects older individuals that causes progressive difficulty with walking, stiffness, slow movement, poor balance, tremor, soft speech and trouble swallowing. Many people also develop cognitive impairment. Destruction of these dopaminergic neurons in the brain leads to many of these manifestations. Notably, any other cause that reduces function of these neurons, like drugs that block dopamine action, may produce similar symptoms. The current gold standard for diagnosis of idiopathic PD is examination of the brain after one dies, and this permits identification of the loss of dopaminergic neurons and abnormal deposition of a protein called alpha-synuclein. Other related diseases like multiple systems atrophy, progressive supranuclear palsy or cortical basal ganglia syndrome may cause similar symptoms but may progress faster than Parkinson disease and respond less well to medications that can provide symptomatic relief to those with idiopathic PD. People with idiopathic PD also may develop cognitive impairment leading to dementia. The dementia may be caused by underlying abnormal deposition of alpha-synuclein in higher brain regions (so-called synucleinopathy) but also could be caused by pathologic changes similar to those that occur in Alzheimer’s disease. In fact those that develop dementia may have Alzheimer’s disease as a cause or an alpha-synucleinopathy with defects in dopaminergic pathways.

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The next relevant point is how dopaminergic pathways are measured in the brain in living humans or animals. A variety of molecular imaging methods have been developed for this. Basically, each of these requires a radiolabeled chemical that is injected intravenously into a person and the radiotracer then enters the brain to more or less selectively stick to some part

of a dopaminergic neuron or gets trapped in the brain by some mechanism related to the integrity of dopaminergic neurons. The goal of such scans is to measure the number or function of these neurons. Some tracers require imaging with positron emission tomography (PET) – relatively expensive but with higher resolution – or with single photon emission computed tomography (SPECT) – lower resolution and less expensive. A fair amount of work has demonstrated that these methods all can distinguish with varying sensitivity a person with PD from a normal subject.

This background information provides the basis for determining what may be the clinical utility of measuring dopaminergic pathways in the brain. Could such measures help with the diagnosis of PD by confirming a defect in the dopaminergic pathways that occurs in PD but perhaps not in some other conditions – like someone with essential tremor – a condition that causes tremor that at times is difficult to distinguish from PD? If so, would this improve patient care? In other words, could we avoid giving someone medicine for PD that is not likely to benefit from it.(Stoessl, 2009) Could the measures help provide prognostic information for individual patients and predict the rate of disease progression? Could such measures help identify those who have dementia due to alpha-synucleinopathy rather than Alzheimer's disease?(McKeith et al., 2007) Can these techniques identify a person at risk for developing PD? Substantial controversy exists as to whether these methods can answer these questions.(Serrano Vicente et al., 2009;Eerola et al., 2005) Many national and international meetings (like the International Movement Disorders Society) have forums for addressing these controversies. In fact, some of these methods have been approved for clinical application in other countries. None had been approved by the FDA for clinical application in this country.

So, this invitation was my opportunity to review the research data that I believe demonstrates no clinical utility at the current time for these molecular neuroimaging methods. After review of the literature I did not believe that the methods helped with diagnosis of PD – the data do not support the notion that it can distinguish PD from related conditions. Some believe that less closely related conditions like essential tremor can be distinguished(Eerola et al., 2005;Ceravolo et al., 2008) but I argued that if there was clinical ambiguity that obscured confident clinical diagnosis between these two conditions in an individual then a simple trial of treatment for PD would be a more direct and far less expensive alternative to a molecular imaging test. Similarly, the only data that supported such techniques to help distinguish causes of dementia were funded by industry that made these types of radiotracers,(McKeith et al., 2007) an arrangement that may bias to reporting only positive outcomes(Kelly, Jr. et al., 2006). In contrast, I do believe that molecular imaging of dopaminergic pathways may be a more sensitive means to identify a defect in these neurons before it can be detected clinically by an appropriately trained neurologist(Marek and Jennings, 2009) – however today we have no treatment that can prevent or slow disease progression to make this a useful clinical tool. In the future, we may have such preventative treatments and then with appropriate selection criteria these types of scan may help identify and treat people to prevent onset of PD symptoms.

So, I decided to participate in this advisory committee meeting. I was told that the agenda would include a basic review of Parkinson disease by Dr. Ted Dawson from Johns Hopkins

University and then I would review the potential clinical utility of neuroimaging dopaminergic pathways in movement disorders. After that there would be presentations by the FDA, presentations by industry and then panel discussion and committee questions.

Everyone arrived at the meeting on time in Silver Spring, Maryland. Dr. Dawson gave an excellent review of Neurodegeneration in PD and then I reviewed the literature on “Neuroimaging of Dopaminergic Neurons: Evidence for Clinical Utility.” In my talk, I also addressed the cost effectiveness of applying molecular imaging for diagnosis compared to a trial of drug – this favored a simple short testing of the response to a drug by a 10 to 1 cost differential. My final slide entitled “Clinical Utility?” included the bullet points that these techniques were not needed for clinical utility and not necessary for treatment decisions in patients.” My conclusions were straightforward.

What then happened? Dr. Dawson and I were invited to observe the remaining talks and sit in the public audience area. We were told that we could not participate in any discussions or ask any questions. The FDA had speakers and GE Healthcare had several speakers justifying their proposal for clinical application of a SPECT radiotracer to measure dopaminergic neurons. We could observe the FDA panel members ask questions of other speakers but we were not allowed to ask or answer questions from the panel or anyone else at that point. Once we sat down after giving our talks, we were prohibited from participation. I must say, I was quite surprised. This permitted several misperceptions to go unanswered. For example, one FDA panel member specifically stated that Dr. Perlmutter supports this clinical application – quite far from my position, but I was not allowed to clarify that point. One of the GE Healthcare representatives presented data from a study that they had sponsored with the conclusion that it was clinically useful to use one of their molecular imaging markers to properly diagnose dementia due to synucleinopathy – a position that I do not endorse. There were multiple questions by panel members that we could have easily addressed but again we were not allowed to respond and they were not permitted to address us. One panel member specifically asked the Chair of the panel whether they could consider cost effectiveness of this drug and was told that was not to be considered in their decision to recommend or not recommend approval of the application from GE Healthcare.

I left that meeting feeling that I was window dressing rather than a considered expert on an important topic. The next week, I learned that the panel voted 11 to 2 to recommend approval of the GE Healthcare application.

What are the business ethics issues raised by this experience. First, I am concerned that there was a lack of interaction between the committee and the invited experts. The playing field was not level. How come? The challenges to the FDA are substantial. There are pressures to approve new drugs that can improve healthcare for Americans. Frequent complaints arise from the public about delays with FDA approval. Yet, we also hear about potential bias from FDA panel members that may have relationships to industry and that the FDA receives a substantial part of its funding from industry sources – the same industry that the FDA regulates (Olsen and Whalen, 2009). These conflicts of interest exist (Kelly, Jr. et al., 2006). I believe that my experience demonstrates one example of where potential bias of information can influence a panel.

In fairness, there are many other movement disorders specialists who believe that these imaging methods would help them make decisions. One such movement disorders specialist also gave a presentation for GE Healthcare at the meeting and made the point that neurologists in other countries can order these molecular imaging tests and we cannot – a deficiency that he thought should be corrected. However, my position is that when the FDA considers such applications, a more thorough and objective review of the data is warranted. The question really is “who wants the truth?”

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