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State of the Art in Pharmacologic Treatment for Alzheimer's Disease

STATE OF THE ART IN PHARMACOLOGIC TREATMENT FOR ALZHEIMER'S DISEASE

ReachMD would like to wish you a happy and healthy New Year and with each New Year comes a fresh start. As we look ahead, ReachMD is proud to present this month's special series Focus on Future Medicine.

Alzheimer disease is a crippling illness that affects so many of our patients. Where is the state of the art in terms of treatment of this disease and what future prospects lie ahead.

Welcome to the Clinician's Roundtable on ReachMD XM160, The Channel for Medical Professionals. I am your host, Dr. Lee Freedman, and with me today is Dr. Samuel Gandy, Professor and Director of the Farber Institute for Neurosciences at Thomas Jefferson University and the Chair of the Medical and Scientific Advisory Council of the Alzheimer Association.

DR. LEE FREEDMAN:

Thank you so much for being with us Dr. Gandy.

DR. SAMUEL GANDY:

Thank you for having me.

DR. LEE FREEDMAN:

In terms of current treatments for Alzheimer's, I think of the acetylcholinesterase inhibitors, can you tell us a little bit about them and what their utility is?

DR. SAMUEL GANDY:

Sure, there are currently four medicines that are approved for therapy for Alzheimer disease, three of those fall into that category of acetylcholinesterase inhibitors and they act by helping the brain compensate at the beginning of the illness for the deficiency in chemical transmitter called acetylcholine in the nerve cells used to talk to one another. For reasons that we don't understand the nerve cells that create acetylcholine as transmitter are especially (**01:30**) vulnerable to the early stages of Alzheimer's and they go on to die and therein lies the reason that medicines wear off. The medicines block or help to slow the breakdown of the transmitter, but they don't actually act directly on the receptors nor can they stimulate creation of the transmitter, so once those nerve cells that are making the substance die, medicines wear off and so we know then that though the medicines seems to help a bit at the beginning of the illness and it's a little while, they do wear off, it's not clear that they have a major impact on the rapidity of the progression of the disease.

DR. LEE FREEDMAN:

So we are not really reversing, we are kind of delaying the process and then once these start wearing off, the decline tends to be exactly at about the same rates?

DR. SAMUEL GANDY:

There is a bit of an acceleration eventually in those people, the things often start out rather slow, but at some point there is an acceleration of a decline in many cases and the cholinesterase inhibitors don't really help stave that off, they help on the sort of latter part of the curve of the progression of the illness, they sort of, one example I use is they sort of turn the clock back 6 months, but the clock then keeps ticking.

DR. LEE FREEDMAN:

So I imagine it's important to start these as early as possible (**03:00**).

DR. SAMUEL GANDY:

They have been approved for all phases of the illness and there does seem to be some benefit even at the late stages, that has only recently been studied, but certainly the classical use is for them at the beginning of the disease to try and down since they only work while those nerve cells are alive their best chance of getting a response, that is why it is in the early stages of disease, why all those cells are still making the acetylcholine?

DR. LEE FREEDMAN:

And then for me as an internist, it's often hard to feel confident in making the diagnosis. I want to start these drugs early, is that a challenge for a lot of people coming up with a firm diagnosis, this is Alzheimer's.

DR. SAMUEL GANDY:

Well, certainly in diagnostic centers, there tends to be a fair degree of certainty in specialized Alzheimer centers the diagnostic accuracy is about 90%, but again that's not a generalist population, that's an Alzheimer center population where we have those numbers and of all of the dementic illnesses, all of the causes of dementia, about two-thirds is Alzheimer's so if you guess Alzheimer's you are almost certainly going to be right two-thirds of the time. Being absolutely confident as at a specialty center is a challenge and that's something that the radiologists and the molecular biologists are trying to attack by developing either brain scans that will help generalists make the diagnosis or blood or spinal fluid tests, usually blood (**04:30**) tests are the most convenient. We don't have those at the moment. So there are two choices, either to begin the drug yourself as an internist or to refer. The good news is that the medicines are really pretty well tolerated and pretty safe so that you don't really have to feel that reluctant about using them, at least in terms of side effects or causing damage. You can get some problems with drooling and GI distress, but it is usually not very severe. One reason to think about though is that as new medicines are coming along to be tested in clinical trials, some are excluding patients who have already been or are currently on acetylcholinesterase inhibitors. We are actually in the midst now of testing a new medicine called <_____> which looks very promising, but the original trial which was done in Russia, the drug treatment group was compared to people who had never taken any drugs at all, the whole population was drug naïve, and so the replication trial before the medicine can be approved by the FDA, there has been so far a tendency even in the states with the replications to exclude people who are on cholinesterase inhibitors.

DR. LEE FREEDMAN:

So not a lot of downside to starting these, but with that caveat that perhaps if you are looking to get someone enrolled in one of the trials that may disqualify them.

DR. SAMUEL GANDY:

That's exactly right. (**06:00**)

DR. LEE FREEDMAN:

And so I imagine we do our typical blood work and some type of brain imaging to rule out the so called reversible causes and then it wouldn't be all that bad, just empirically to start on an acetylcholinesterase inhibitor.

DR. SAMUEL GANDY:

That's what is typically done by family physicians and internists throughout the country. There is usually an MRI these days to exclude you know something that might be treatable like a say hydrocephalus, normal pressure hydrocephalus is one of the things that can mimic Alzheimer's disease and the blood tests to exclude some metabolic cause, thyroid dysfunction, other endocrine abnormalities can mimic Alzheimer's and chronic cerebrovascular disease, I mean, rare illnesses can mimic Alzheimer's and would then dictate a different therapy, but if you can't find anything medically wrong, the most likely cause is Alzheimer's. Out of that remaining thirds, the two-thirds is Alzheimer's, the remaining third, about half is a somewhat different disease called frontotemporal dementia and we have begun to recognize this more and more and it's not a rare cause of dementia and there are estimates sort of early days in getting good numbers, but there are estimates that in the younger onset population of dementia, that frontotemporal dementia before age 65 may be just as common as Alzheimer's.

DR. LEE FREEDMAN:

Dr. Gandy, I imagine Namenda (**07:30**) is that fourth approved drug. Where does that fit in, should it be started first to mitigate the GI

side effects of the acetylcholinesterase inhibitors, how do you feel about Namenda?

DR. SAMUEL GANDY:

Namenda is often started early. It's really most intended for moderate stage disease. The mechanism is to block the type of receptors that are involved in the phenomenon called excitotoxicity. If glutamate receptors are stimulated too much, they can actually cause nerve cells to die and Namenda interferes with that and that the tendency for nerve cell to die in the presence of glutamate, the nerve cells are sensitized if there are the characteristic amyloid plaque of Alzheimer's around the brain, so the nerve cells with plaques around it is oversensitive to glutamate toxicity, that's how we think we are doing with Namenda.

DR. LEE FREEDMAN:

And using these medications either together or independently are we talking about clinically important benefits or just benefits on certain statistical tests?

DR. SAMUEL GANDY:

It's fairly controversial. I think that there clearly are individuals, who have dramatic responses. I would may not say moderately dramatic response, I mean obviously where the entire family says things are different and there is a clear response. In many cases, there is not much of a noticeable response, may be on a neuropsychological test, but really not much in the way of clinically important (**09:00**). The problem is that there is no way to predict whether a person will respond or won't and once the drugs are started, the family and/or the physician tend to be reluctant to withdraw them thinking that they might be doing something and if we stop them, things will get worse, so it's not a very satisfactory situation as you know from your practice, but the real striving with the use of the drugs is the fact that sometimes unpredictably there are fairly remarkable responses and those are the times obviously that we want, but they are probably not the majority of people who get the drugs.

DR. LEE FREEDMAN:

Now sometimes when I will send a patient for a specialty consultation for this, they will come back on certain vitamins or natural things, folic acid derivatives, alpha lipoic acid, is there data to support the use of these products?

DR. SAMUEL GANDY:

There is a lot of interest and they are all of diet and lifestyle in the risks for Alzheimer's and there are epidemiological links to what's called the Mediterranean diet that's rich in fish oil and vegetables and this has a connection with red wine and may be that also seems to might delay the onset. The problem is that in every case, I guess with the exception of vitamin E, which has been tested and failed, these are epidemiological studies and they haven't been subjected to randomized clinical trials. So we don't know for sure whether (**10:30**) these epi-studies are giving us reliable information or not. We have had epi-data on hormone replacement therapy that misled us and epi-data on statins that seemed to have misled us. Most of these things tend to be the vitamins, alpha lipoic acid, or omega fatty acids. They are things certainly aren't bad for you, may be good for you, so we can since they are not prescription medicines and perhaps not focus on them as much as we might on a prescription medicine, but we really don't have the data to say which of those you should take and how much you should take. It's really sort of a little voodooish.

DR. LEE FREEDMAN:

But again, very little downside I suppose to trying these.

DR. SAMUEL GANDY:

The downsides come if this is a person that you think might go to a clinical trial. I mean, for example, there is a medicine that is being tested down. It involves the inflammatory response in breaking down amyloid and people, who are taking nonsteroidals have to come off for at least 3 months so that they can start that trial and given the fact that nonsteroidals don't show a dramatic benefit, there is not a compelling reason to start them. Especially if someone is going for clinical trial. So those are the only downside as it sometimes people begin things that you think will be good for you anyway even if they don't help prevent Alzheimer's, they might complicate their ability to get into a clinical trial. If there is someone who think is definitely (12:00) not going to a clinical trial, there is usually no harm in it, but again there is no compelling evidence for either end. If you have people who are taking 12 different pills a day and 10 of them are useless, it sorts of puts a strain on the caregiver as well to try and get things right.

DR. LEE FREEDMAN:

I want to thank Dr. Samuel Gandy, Professor and Director of the Farber Institute for Neurosciences at the Thomas Jefferson University and Chair of the Medical and Scientific Advisory Council of the Alzheimer's Association for kind of going through with us the state of the art for pharmacologic treatment for Alzheimer disease. This has been the Clinician's Roundtable on ReachMD XM160, The Channel for Medical Professionals. Thank you very much for listening.

Thank you for listening to ReachMD on XM160 and this month's special series Focus on Future Medicine.

You are listening to ReachMD, The Channel for Medical Professionals. Welcome to Patient Safety News provided by the Food and Drug Administration, the FDA, Protecting and Promoting the Public Health. Today's highlight is hosted by Mark Barnett and Anita Reiner.

MARK BARNETT:

Covidien and Mallinckrodt, the manufacturers of Phosphocol P-32 have informed healthcare professionals that this drug may increase the risk of leukemia in certain situations. Phosphocol P-32 is used to treat peritoneal or pleural effusions in patients with metastatic cancer if instilled into the peritoneal or pleural cavities where it (13:30) locally irradiates tissues.

ANITA REINER:

The manufacturers report that two children ages 9 and 14 developed acute lymphocytic leukemia about 10 months after they received Phosphocol P-32 by intra-articular injection. Phosphocol P-32 is not indicated for intra-articular injection in treating hemarthrosis and its safety and effectiveness in children have not been established.

ANITA REINER:

OSI Pharmaceuticals and Genentech are alerting healthcare professionals about hepatic failure and hepatorenal syndrome with the use of Tarceva particularly in patients with baseline hepatic impairment. Tarceva is erlotinib and is approved to treat certain patients with lung or pancreatic cancer.

MARK BARNETT:

Patients with hepatic impairment who are treated with Tarceva should be closely monitored during therapy. Treatment should be interrupted or discontinued if patients have severe changes in liver function. Tarceva should be used with extra caution in patients with total bilirubin that's greater than 3 times the upper limit of normal. You can get more information by going to our website.

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