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Ginkgo Biloba: How Supportive is the Data?

#### USE OF GINKGO BILOBA SUPPLEMENTATION TO POSSIBLY ENHANCE COGNITION

Patients looking for the Holy Grail for cognitive improvement have been using Ginkgo biloba for many years to the tune of over a billion dollars per year. What is the data to support this use? Welcome to the clinician's roundtable. I am Dr. Leslie Lundt, your host, and with me today is Dr. Jeffrey Kaye. Dr. Kaye is Professor of Neurology and Biomedical Engineering at Oregon Health and Science University. He also directs The Layton Aging and Alzheimer's Disease Center at Oregon Health and Science University as well as being the Director of Geriatric Neurology at the Portland VA Medical Center. One more job he has is to direct the Oregon Center for Aging and Technology.

**DR. LESLIE LUNDT:**

Welcome to Reach MD, Dr. Kaye.

**DR. JEFFREY KAYE:**

Thank you very much.

**DR. LESLIE LUNDT:**

You're a busy guy?

**DR. JEFFREY KAYE:**

I enjoy what I do.

**DR. LESLIE LUNDT:**

That's great. Now, tell us about Ginkgo biloba. Why has it been used over the years to help cognition?

**DR. JEFFREY KAYE:**

Well, I think there are number of reasons. First of all, there are no really good treatments for Alzheimer's disease or dementias, and people are in some ways, I think a little bit desperate sometimes to find something that will help. I think there are a lot of people who fear getting dementia and so even a lot of normal elderly will, or not even elderly people, day bloomers will take supplements of various kinds in hopes that they would ward off dementia at some later day.

**DR. LESLIE LUNDT:**

So the lack of reasonable alternatives and everybody is afraid.

**DR. JEFFREY KAYE:**

I believe that is the reason that the public in general is taking these (01:30) various compounds, in particular Ginkgo, but I also think that there has been probably a little more scientific background to at least suggest that there might be some benefit to Ginkgo.

**DR. LESLIE LUNDT:**

Tell us about your work in this area.

**DR. JEFFREY KAYE:**

Well, I've been very interested in Alzheimer's disease and actually brain aging for many years. I have been spending a lot of time in my career looking at mechanisms for why people actually don't get demented, what protects them from getting demented, and so along the way, I have been very interested in treatments or other passways that might lead us to not years to life, but life to years.

**DR. LESLIE LUNDT:**

So, you recently published a review of the Ginkgo research. What did you find?

**DR. JEFFREY KAYE:**

Well, actually several years ago, with a colleague of mine in OHSU, Dr. Barry Oken, we reviewed the literature on this; the randomized controlled trials that had been performed, and there was a handful of that at that time that met a reasonable criteria were well-conducted studies, and there was a suggestion in fact that maybe on balance, there might be some positive effect, but all the studies unless they had certain limitations. So, realizing that, and a growing interest in alternative medicines, particularly even the NIH, which in the last decade has established this, actually a National Center for Complimentary and Alternative Medicine. We applied at NIH that we try to begin to do a study (03:00) of Ginkgo biloba as a preventative for dementia. So, just to highlight, we were really trying to set the stage for how this compound or extract really because it is not a pure drug, might prevent the onset of cognitive decline, not actually use it for people who already had manifested dementia or Alzheimer's disease. So in order to begin to do that, one of the great interests was to try to shorten the development cycle if you will because fortunately as it turns out for normal elderly, the rate of developing cognitive

impairment is not terribly high, that is particularly if you are 65 or 70, only may be 1% to 2% at most of the population will develop cognitive impairment or dementia in a given year. So you can imagine if you wanted to look at individuals who would be prevented from progressing, you would have to have thousands of individuals in order to change that very small conversion rate over time, and so one mechanism for trying to overcome that, if you will, low conversion rate for the purposes of proving that a treatment such as Ginkgo might work as a preventative, was to raise the age at which we followed people. So, the incidence of dementia essentially doubles with each successive decade and so by focussing on people 85 and older, we reason that we might actually be able to increase the rate of potential conversions of dementia (04:30) within a grand cycle as funded by the NIH. So, with that sort of concept in mind, we designed what we called a Proof Of Concept Clinical Trial for the prevention, and enrolled 134 people who were randomized to a Ginkgo treatment or a placebo and then they were followed for 36 months to see in fact whether we had more people who converted to the cognitive impaired group or not over that time.

**DR. LESLIE LUNDT:**

So, quite a long time, 36 months.

**DR. JEFFREY KAYE:**

Actually, it was 42 months. If I said 32, it was actually 42 months, in fact even longer. This was considered at the time truly prove the concept because maybe would say, first of all no one had ever done a clinical trial that was focused on the so-called oldest old, people 85 and older; and furthermore could you actually consistently follow a group of people in that age group over 42 months. And, so the first answer was in fact, we definitely could and we did, and we had very a little dropout over that time period. Interestingly, one of the things that we found was that many of these older people that we approached to into the trial would say things like "Sure, we're happy to help. No one thinks we can do anything at our age."

**DR. LESLIE LUNDT:**

Hmm.

**DR. JEFFREY KAYE:**

And then, over time, they were very committed people to staying in the project if they were able to.

**DR. LESLIE LUNDT:**

And what's the downside of using Ginkgo in terms of side effects?

**DR. JEFFREY KAYE:**

Well, as in any clinical trial, we were particularly interested in monitoring for side effects. One of the most important side effects (06:00) that has been around and publicized was a potential concern about bleeding risks or hemorrhagic side effects, and this is basically, I think based on a number of case reports that had appeared in the literature that were of concern, although collectively if one looks at the clinical trial that had been done using Ginkgo extracts over many years, I do not really think there has ever been a real excessive

bleeding risks clearly found in those trials. Nevertheless, this was of great concern and we took this very seriously. As it turned out in our trial, we had an excess of strokes, but these were not hemorrhagic or bleeding kinds of strokes. These were actually ischemic strokes. There was one hemorrhagic stroke, but all the others were of the ischemic variety. So, we honestly don't know what to make of that. It was not an expected outcome, but it is something that we certainly, in the course of our studies, observed and noted in our publication.

**DR. LESLIE LUNDT:**

If you are joining us, you are listening to the clinician's roundtable on ReachMD XM 157, the channel for medical professionals. I am Dr. Leslie Lundt, your host and with me today is Dr. Jeffrey Kaye. Dr. Kaye's research program has focused over the past 2 decades on the question of why some individuals remain protected from dementia at advanced stages while others succumb at much earlier times. We are discussing his research looking into Ginkgo biloba and cognition. (07:30)

So, Dr. Kay, what did you find out of?

**DR. JEFFREY KAYE:**

Well, what we found was, in what is the standard of analysis in randomized clinical trials and intense treatment analysis, there was no reduced risk of progression to cognitive impairment whether somebody had been randomized to Ginkgo or not. However, the thing that was tantalizing about this trial, which was known to be under powered to start with because it was a proof of concept trial and not a definitive trial, was that in a secondary analysis when we controlled for the level of medication adherence among the group, that is, the number of people who had remembered to take the medicine properly based on the first 6 months of the trial, there was a significant difference and this is I think is an extremely important principle that should not be lost in the sort of technical jargon of analysis of the trial, and why I think this is very important is that all of the cognitive prevention trials that are ongoing or planned really need to take this into account prior to analyzing their data. So if you think about it, in a prevention trial for dementia, you are basically enrolling people who are normal. You do not have a collateral informant and somebody who is following along with you as you would have in a dementia trial. You have the person themselves reporting on how they are doing. They are also themselves reporting on how well they are taking medications. If their memory is declining as they progress through the trial, their ability to report their level of adherence to the medication regimen is going to be impaired progressively. (09:00) If you don't take that into account in the analysis as the trial progresses, you can falsely believe that in fact there was no effect because the person is saying, "Oh, I'm fine, I'm taking all the medication" when in fact, they are not. The other thing that I think is <\_\_\_\_> again not to get into the weeds of statistical analysis, but this study only randomized 134 individuals and actually 118 were actually completed this study. And, although statistically not significant, if you look at the number of people who converted to cognitive impairment over the 42 months who were taking Ginkgo, there were 7 individuals. Among the placebo group, there were 14. So, I think what that tells you is that technically there was a 50% reduction in the incidence of dementia if you will or cognitive impairment over the course of the study, but we did not have the statistical power to really prove that. What this really helps us with though is that as a statistician, one can do the math and in fact we now know, based on this study, that one would need about 300 people in a similar trial to definitively prove or not whether this actually is a treatment that could prevent the rate of cognitive decline in the elderly.

**DR. LESLIE LUNDT:**

What do you currently recommend to your patients who are anxious to help their cognition?

**DR. JEFFREY KAYE:**

Well, it is a very difficult science I think. If you have a strict interpretation list, then you would say based on this trial, there is not definitive evidence. (01:30) I think if you look out across all of the trials out there, there is some evidence to suggest that there is a positive effect, and I think that this is one of those areas where based on the person's health, their financial situation, because people can actually spend hundreds of dollars on alternative medicines, one can suggest if you think this is something you want to do, it is probably reasonable, although again we feel obligated to say in this one study, we did find more strokes in the treatment group. Again, going back to the issue of statistical power, if we had one stroke in the placebo group, there would have been no statistically significant difference in the two groups. So, again we are talking about issues where we are trying to give advice based on data that is not definitive yet. I should say, and I think that listeners really need to know, that there are currently two very large or large studies that are hoored in the 100s that should give us a more definitive result. One is called the GEM study, which is being conducted in The United States; and the other is called GuidAge Study, which is a European study, and these are both randomized controlled trials. They are being done in younger patients, or younger people. In one group, there are over 70; in the other there are over 75, and there will be potentially some differences in the dosing, but at least we are very hopeful that these trials may give us some other direction as to how to advise our patients.

**DR. LESLIE LUNDT:**

(12:00) So hopefully, we will know more by the time I'm 70.

**DR. JEFFREY KAYE:**

Well, I certainly hope we all do.

**DR. LESLIE LUNDT:**

Great, thanks for being on the show today.

**DR. JEFFREY KAYE:**

I really appreciate it. Thank you.

**DR. LESLIE LUNDT:**

We have been discussing the use of Ginkgo biloba supplementation to possibly enhance cognition with Dr. Jeffrey Kaye.

I am Dr. Leslie Lundt. You have been listening to the clinician's roundtable on Reach MD at XM 157, the channel for medical professionals. To listen to our on-demand library, visit us at [www.reachmd.com](http://www.reachmd.com). If you register with the promo code radio, you can receive 6 months' free Internet streaming of the show for your home or office. If you have questions or comments, please call us at 888-MDXM-157. Thank you for listening.