UsAgainstAlzheimer's

Alzheimer's Talks Transcript
Depression and Alzheimer's
with Dr. Scott Mackin

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Note: This transcript has been edited for content and clarity

Welcome to Alzheimer's Talks. This is a monthly teleconference series presented by UsAgainstAlzheimer's. We connect you every month with leaders in research and policy who, like you, are committed to stopping Alzheimer's.

My name is Debra Lappin. I work with UsAgainstAlzheimer's, an entrepreneurial and innovative organization that's transforming the nation's fight against this disease. And it's a real privilege to be here today with you. Thank you for joining us today to hear from Dr. Scott Mackin about a fascinating study.

I only have a few comments before I introduce Dr. Mackin and we get on with the main show. I want to remind you that on September 30 and October 1, UsAgainstAlzheimer's and its networks will host its annual Out of the Shadows Summit and Congressional Hill Day to accelerate progress and to get our message to the Capitol. The two-day summit will bring together national and international leaders in Alzheimer's advocacy and science and we will share data and exchange knowledge and ideas with our policymakers. It would be terrific if you could join us. For more information, or to register, I ask you to go to www.UsAgainstAlzheimers.org and sign up. We know we can stop this disease, but not without a massive united effort. So please consider joining us in September.

Today, we have just under four hundred people registered for the call from about forty-four states, plus D.C., along with individuals joining us from as far away as Russia and London.

If you have a question during Dr. Mackin's presentation, please press *3 on your phone. By pressing *3, you will be placed into a question queue. Please have your question ready to share with a member of our staff, and then we will try to get you live on the air to ask the question, and we hope you'll do this. If you are listening online, you can type your question into the box, and we will get as many of the online questions as possible also keyed up for Dr. Mackin. We're not able to answer calls on specific medical conditions. I think that may be obvious, but I just wanted to stress that.

So, now for our interesting interview and our presentation by Dr. Mackin. It's my pleasure to introduce you to Scott Mackin. He is an Associate Professor in the Department of Psychiatry at the University of California San Francisco School of Medicine. He is the lead Scientific Investigator for the Brain Health Registry (which we discussed here in a previous Alzheimer's Talks) and he is a Principal Investigator for the Alzheimer's Disease Neuroimaging Initiative Depression Project (ADNI-D). His research has focused on a wide range of neurodegenerative diseases including Alzheimer's, dementia, late life depression, and traumatic brain injury.

Dr. Mackin, thank you so much for joining us today. We look forward to hearing more about the ADNI-D study, and your work specifically on late life depression and Alzheimer's.

Dr. Mackin: Thank you so much, Debra, it's really a pleasure to be here talking with everybody. I look forward to the call today and the questions, hopefully, that follow.

So what we will be talking about today is a new study, as you mentioned. The study name is Characterizing Cognitive Decline in Late Life Depression, the ADNI Depression Project. Really this work stemmed from early interest in my career, when I worked at the UC Davis Alzheimer's Disease Center, and I was struck by the number of patients that were coming in for evaluations for Alzheimer's disease, by the high rates of depression that we were seeing in these patients, as well as the impact that depression had on their cognitive symptoms as well as functional symptoms, and also how it appeared to impact the progression of Alzheimer's disease.

At that time, there were several things that were missing from the field of research that hopefully we can address, in some part, with our new study. One of the largest barriers to understanding how depression might influence the progression of Alzheimer's disease is that currently, individuals with major depression are often excluded from studies of Alzheimer's disease. And we'll talk a little bit more about why that's the case, but that's a factor that has really limited our ability to better understand how depression impacts Alzheimer's disease.

Other limitations included that the existing studies tended to be fairly small and have a limited number of clinical variables that they could investigate. This is because these are very expensive trials, and we were hoping to find a way to address that issue as well. And then perhaps most importantly, is that many of these studies were difficult to compare across sites, because people were using different study protocols, they weren't using consistent approaches. Therefore we had a number of studies being conducted, and it was very hard to put all those results together.

And that's one of the primary things that we're hoping to address in the ADNI Depression study, is a mechanism to freely share data with researchers worldwide, using consistent approaches, so that our data can better inform our understanding of how depression impacts cognitive decline in older adults, as well as Alzheimer's disease.

We have, in our study, several specific hypotheses about what the association between depression and Alzheimer's could look like. The key areas that we are interested in are studies of cerebral blood flow, cortical atrophy, and amyloid deposition. So we'll talk about all of these things in context in just a few moments.

I do want to point out that this study was made possible, first, through funding through the National Institute of Mental Health, which we're very grateful for. We're also very grateful for our partnership with the Alzheimer's Disease Neuroimaging Initiative, and the PI [Principal Investigator] for that study is a friend and colleague Mike Weiner. And the ADNI project, it's probably familiar to many of your callers, but just very briefly, ADNI was started in 2004, and currently has over fifty-five sites in the U.S. and Canada, studying over a thousand participants with either normal cognitive function, mild cognitive impairment, or Alzheimer's disease. And really, the key objective for ADNI is to better understand what causes Alzheimer's disease in an effort to identify prevention and treatment strategies.

ADNI focuses on looking at several different areas, including cognitive function, structural and functional brain abnormalities, as well as biomarkers. By partnering with ADNI, and using the exact same procedures, allows us to compare data that we're collecting with the data that's already been collected in ADNI. This offers a tremendous opportunity for us to leverage, or build upon, the work that's been done by ADNI, and allows us to use data that they've collected as comparisons and to answer questions that we have about our sample, which will focus on individuals with late life depression.

Our goal for the ADNI Depression Project is both to ultimately inform treatment and prevention strategies for depression but then also: How does this impact the progression of Alzheimer's disease? To start at the very beginning: Depression can mean a lot of things to a lot of different people. So very briefly, when we're talking about depression, we're talking about clinically significant depression, which is characterized by consistent or protracted feelings of depressed mood, loss of interest, it can also include weight change, changes in sleep, feelings of fatigue or loss of energy, feelings of guilt or worthlessness, as well as cognitive symptoms, primarily concentration difficulties, or difficulties with indecisiveness. A key feature of depression is that these symptoms are consistent so they're occurring more days than not, it's not a reaction to a specific event that passes relatively quickly. We're looking at a stable pattern of symptoms over time.

Depression is one of the leading causes of lifetime disability worldwide, it's extremely prevalent; estimates in older adults suggest that up to about fifteen percent of older adults suffer from major depression or clinically significant depression. The economic cost of major depression worldwide is staggering. This is a big public health concern, and often, the cognitive symptoms and functional symptoms in depression in older adults often overlap what we see in the early stages of Alzheimer's disease. And this is the reason why they're often excluded from studies of Alzheimer's disease, because investigators, when they're looking at specific mechanisms for Alzheimer's disease, they don't want to have other diseases that potentially could create the same types of symptoms and make it more difficult to understand their data. This is unfortunately a limitation, because it does not allow us to investigate the potential role of depression on the progression of Alzheimer's disease if we're routinely screening these patients out of the studies.

So, we know that depression is very common in older adults. It's very debilitating. One of the key features of depression in older adults is that it has an impact on social or functional status, so a depressed mood actually impacts ability to complete activities of daily living or do the things that they would normally be doing. But we also know that cognitive impairments are very common in older adults with depression. Best estimates would suggest that about sixty percent of patients with late life depression also have some form of mild cognitive impairment. These cognitive impairments can occur in memory, they could occur in information processing speed or attention, so there's a wide range of cognitive impairments that are frequently common in late life depression. These are also symptoms that are very common in the early stages of Alzheimer's disease, particularly memory problems or executive problems that we see in the early stage of Alzheimer's disease, we're also seeing in late life depression.

Now, as I mentioned before, about fifteen percent of older adults suffer from clinically significant depression. However, if we take a sample of people who are coming in for an evaluation for Alzheimer's disease, if they maybe have mild cognitive impairment or Alzheimer's disease, that number increases to over fifty percent. And this suggests that there's a shared mechanism, potentially, that overlaps late life depression and neurodegenerative conditions, specifically Alzheimer's disease.

Unlike Alzheimer's disease, we do have several effective treatments for depression, and when we treat depression and these symptoms go into remission, we can look at how people's cognitive functions change over time, and this data suggests that many of the cognitive symptoms that we see in older adults with late life depression are chronic so they don't necessarily improve with treatment of depression, but some do. And most of the improvements are seen in the domain of information processing speed, and we're going to come back to that in just a minute.

But other relevant research worth noting is that late life depression has been consistently shown to be associated with more rapid rates of cognitive decline in older adults as well as more rapid conversion to dementia. And as a result, depression is often viewed as either a risk factor for dementia, or a concurrent feature of dementia, or some combination. The exact mechanisms are not known, and that's one of the reasons that we're conducting this study, to get a better sense of what the underlying mechanisms are that potentially link depression and Alzheimer's disease.

So there are several key areas, and I'll go through these relatively quickly, and we can follow up with any questions.

There are several key areas that are important as we discuss the potential overlap between late life depression and Alzheimer's disease. They include: white matter lesions, cortical atrophy, cerebral blood flow, amyloid deposition, and biomarkers. So I'll go through each one of them relatively quickly just to provide a framework for why we're conducting this study.

With respect to white matter lesions: If we think of white matter lesions as connective pathways of the brain, connecting different cortical regions that are necessary for complex thought, depression in older adults has been strongly linked to vascular lesions. It's referred to often as vascular depression and it typically is a syndrome where people might more commonly have a late onset of depression, so perhaps have not had depression throughout their life, as they get older they have a later onset of depression. And the reason for this is these white matter lesions, which tend to impact the frontal striatal brain lesions, are thought to have a negative impact on the production and regulation of neurotransmitters that impact mood.

These white matter lesions have also been linked to information processing speed deficits, and some data suggests that vascular depression is more difficult to treat with antidepressants. Now we know that progression of white matter lesions might impact cortical atrophy or amyloid deposition but there haven't been a lot of studies that have really specifically looked at this in late life depression, and that's one of the goals that we have for our study. So by partnering, again, with the ADNI infrastructure, we can enroll patients into our study who are depressed and compare our findings with a large number of individuals that are either cognitively healthy, have mildly cognitive impairments, or Alzheimer's, to better clarify what's the link between vascular disease and depression, as well as what's the link between vascular disease and cognitive impairments that might serve as a basis for this shared mechanism between Alzheimer's disease and late life depression.

In addition to white matter lesions, there's an emerging literature to suggest that there are cortical abnormalities among individuals with late life depression—and when I'm talking about cortical regions, we're talking about the outside layer of the brain that is used for higher order thinking, memory processing. Some of our early data, as well as data from other researchers, suggests that late life depression could cause cortical

atrophy in older adults. It's also possible that the cortical atrophy is causing the symptoms of depression, so we need to untangle that relationship. But at present, there's significant evidence to suggest that there is a link between depression in older adults and cortical atrophy. And this is a key area of study for our new project.

In particular, we're looking at frontal brain regions, as well as the hippocampus, and, as you are all probably familiar, the hippocampus is a very important structure for memory and is impacted by Alzheimer's disease. We really want to use this study to get a better or more clear understanding of how late life depression might be impacting cortical abnormalities that could hasten the progression of Alzheimer's disease.

We've also done some work that's showing how these cortical abnormalities are associated with poor treatment outcomes for depression, but because, again, these studies are very expensive, the existing studies have been very small with respect to sample size, and most do not have a well-characterized comparison group of individuals with Alzheimer's disease or mild cognitive impairment. This is something that we're hoping to address, again, with the ADNI Depression Project.

So, in addition to white matter lesions and cortical atrophy, something that we're very interested in, in our lab here, is what's the relationship between cerebral blood flow and depression, and potentially, Alzheimer's disease? Cerebral blood flow is important for healthy brain functions, so essentially what I'm referring to is how much blood is the brain getting? That's important for brain metabolism, which is important for keeping all of our cognitive functions as sharp as they can be. Some of our early data suggests that a key feature of late life depression might actually be reductions in cerebral blood flow, and some of our early work also shows that with successful treatment, the level of blood flow returns to normal. So there's a few data points that suggest that reductions in blood flow might be a key feature of late life depression, and that when depression is treated, it reverts back to normal. What we're interested in is testing some of these hypotheses in a larger sample, but then also, to evaluate what's the potential role of reduced blood flow in cortical atrophy as well as the deposition of amyloid in the brain.

That brings us to amyloid, again, which is a key feature of Alzheimer's disease. It's often used as a marker of Alzheimer's progression. We still currently don't know if amyloid is causing the cortical atrophy and the cognitive symptoms that we're seeing in Alzheimer's disease, but there is evidence that suggests that it's a key feature.

To date, there have been very few studies that have looked at amyloid production and amyloid deposition in older adults with late life depression. Because we know that individuals with depression often have a faster course in progression to dementia, this is something that we're very interested in getting a better understanding of. Our colleague at the University of Pittsburgh, Dr. Meryl Butters, has been working in this area for some time. She'll be publishing a paper, hopefully in the next few months, of a recent trial that she has conducted, and this is a central area for our current investigation, where we'll be looking at how older adults with depression and how, potentially, amyloid deposition is linked to depression.

Similarly, a colleague and co-investigator, Dr. Yvette Sheline, published some data earlier this year, that suggests that certain types of antidepressants might actually decrease plaque formation, and she published some data in both mouse models and human studies. The human studies are small samples so we're hoping that we can build upon those with our current study and get a better sense of how treatment history, as well as just history of depression, might be linked to amyloid deposition.

And I am going to be cognizant of the time—I realize I am almost out of time—so I will just briefly mention that another key area for our investigation is to collect genetic data and biomarker data for our sample of older adults with depression. These types of studies often require very large sample sizes, so our hope is that we collect this data, we make it available to researchers worldwide so the data can be combined with other data sets, to get a better understanding of how biomarkers and genetics influence both depression and of course Alzheimer's disease.

Very briefly: our study, I think, has several different innovative characteristics. One is that we are collecting data using the same platform that the larger ADNI study uses. This enables us to compare our results with their samples. We're also using the approach that Dr. Weiner pioneered with respect to making this data freely available to researchers worldwide. All of the data collected for this study will be deposited in a data set that researchers worldwide can access, and test hypotheses using this data. Our hope, is that will improve the time to which we can make scientific discovery and hopefully, again, prevent, or add to the discussion of treatments for, Alzheimer's disease.

Our study will be conducted at two locations. We'll be enrolling participants at the University of California at San Francisco; the phone number for the coordinating center here is 415-476-7046. We're also enrolling subjects at the Pittsburgh Medical Center. Their phone number is 412-246-6487.

I do realize that not everyone on the call is close to a recruitment center for this specific project, but as Debra mentioned earlier, I'm also a co-investigator for the Brain Health Registry, which was featured on a previous call. The advantage of the Brain Health Registry is that it's an online or internet-based research registry for people interested in participating in studies of Alzheimer's disease, cognitive decline, depression. The Brain Health Registry is really open to anyone who might be interested in any type of study of brain health, regardless of age or location. The web site is www.BrainHealthRegistry.org so if you'd like, you can log on to that registry and sign up there, and then if there are studies in your area, then you can be contacted for those studies as well. We are working with the Brain Health Registry specifically on studies of depression, so this is something—perhaps if you're not close to a location for the ADNI Depression Project—you'd consider joining the Brain Health Registry.

I believe I am right up against the time. I suppose I should mention study participation involves several appointments; individuals will be paid for their participation; and again, all of the de-identified data goes to a central location to be made available to researchers worldwide.

I think this point is where I stop and we potentially open up to questions.

Debra Lappin: Dr Mackin, thank you. What a contribution to science and to the health of aging Americans you are making. I think I speak for everybody on the phone. Just hearing the depth and the immediacy, the importance of the questions that you are asking, for anybody who's had somebody with Alzheimer's in their family, the recognition of the role of depression and the frustration with not knowing how to treat the depression as well as the cognitive impairment. I think you're going to hear, in the questions that follow, a real interest in digging down into exactly the advice for our callers that you may be able to give.

So, let me begin with some of the questions that we've received. Dr. Mackin, you've said that late life depression is associated in ways that you're studying with a more rapid

rate of decline. The question is, then, does getting depression treated versus not being treated, make a difference in delaying cognitive decline? Can you tease that out a bit more?

Dr. Mackin: Absolutely. That's a great question; it's not an easy question to answer but I will answer it to the best of my ability.

Right now, our current understanding is, if we go back and we look at the characteristics or the symptoms of depression, cognitive symptoms are part of the symptomatology of depression as well as functional declines are required for a diagnosis of depression. So if someone has major depression, we know that very often they will have some cognitive symptoms associated with depression itself, and they will have some functional impairments associated with depression. Now, treating the depression, kind of acutely, does impact cognitive function, so we do have data showing that if someone is treated for depression relatively quickly, for a large number of individuals, we'll see improvements in some areas of cognition. And that tends to be in speed of information processing, so how quickly can people process information, which, as you can imagine, has a potentially large impact on their daily functioning, because just about everything that we're doing, throughout our day, requires us to process information; often we have to process things quickly.

So, there are two essential answers to that question. One is, having depression treated is important, aside from the fact that it can give relief from the symptoms of depression. It does tend to have improvements in cognition. The question that we don't have the best handle on at this point is for someone who's maybe had a lifetime history of depression, and different treatments, how that potentially might influence the progression of Alzheimer's disease. That's one of the questions that we're hoping to answer with this study. We'll spend a lot of time with participants asking them about their lifetime history of depression, all of the different types of treatments that they've had, so that we can then look at that in a forward way, so a prospective way, to see how that potentially impacts cognitive decline in the future.

Debra Lappin: Very good, because several people had sent in a question, what about earlier history of depression, from a much younger age, so I gather from your response that's a key part of your study, late life depression versus a life long history of depression, very important.

Let me ask this question. It comes from Tracy Jones, online, a very good question: Will the research look at how race, gender, or environment, rural versus urban, affect Alzheimer's disease patients as well as those with late life depression?

Dr. Mackin: Well, we hope the answer to that would be yes. Now, a couple of key clarifications. So what we're doing is, we're enrolling a subset of patients, or a sample of patients, that will all meet criteria for current major depression, and I probably should have spent a little bit more time on this earlier. So the patients that we're enrolling will all be depressed and cannot have a diagnosis of Alzheimer's disease when they enter the study. The reason for that is because we're trying to build out this data set and compare to the existing ADNI data that does have people with the diagnosis of Alzheimer's disease or mild cognitive impairment. So in doing that, we have the ability to look specifically within our depressed sample and to see how things like gender, race, ethnicity, impact the course of cognitive decline. It will also enable researchers who are accessing the larger ADNI data set to include our data, to look at how depressive symptoms might influence the course of Alzheimer's disease. But it is important to note that we're enrolling patients with late life depression without a current diagnosis of

Alzheimer's disease into the study, with the goal of following them prospectively. And the last part of that question was, I believe, the role of where a person is living, whether it's urban versus rural. So that's something that potentially could be looked at using locations for individuals in the study. We have not done too much with that, in our lab yet, but it's certainly possible that those questions could be answered because we are collecting that data.

Debra Lappin: Several people have said, and I'll read one from Virginia in Wyoming: "I am genetically loaded for Alzheimer's. I suffer from depression (I hope that was all right, Virginia, you allowed us to say so), I'm sixty-six and I want to volunteer for a study." I think it's just very important for this call: Is the Brain Health Registry, the route for somebody such as Virginia to find a study and to become actively involved in research?

Dr. Mackin: Yes. It's an ideal mechanism. The goal for the Brain Health Registry really was to address this very issue. Most existing research registries tend to be tied to a specific disease or patient population. The Brain Health Registry and the approach that we took there was to get more general, so that anyone who's interested in participating in studies of brain health, cognitive function, can go to the web site, again it's www.BrainHealthRegistry.org. They can learn more about that registry; it is an excellent opportunity too. You answer questions on the web site, we also have online cognitive tests, so we can actually evaluate cognitive functioning online, and then, depending on the individual's interests or what they would be amenable to, we could follow up and say we're conducting a study on this, would you potentially be interested, or, there's a clinical trial in your area for Alzheimer's disease or depression, would you be interested in hearing more? And so we give individuals the opportunity to hear more; there's no commitment when they sign up, but essentially the goal was to provide more information for studies that are either occurring in their area or studies that can be done online if they have online access.

Debra Lappin: Excellent. Question from Shawn Taylor. Is anxiety included in the definition of depression? And could you repeat the age parameters for the study? I don't know that you gave those to us; you talk about late life but you haven't given us age parameters.

Dr. Mackin: Absolutely. I will start by saying that for our study we're looking at individuals who are sixty-five years or older, who are currently experiencing symptoms of depression, and do not have a diagnosis of Alzheimer's disease. We also request that they have a study partner or an informant that can act as another source of information about the participant's day-to-day functioning but this isn't required. So it's great if we have that, but it's not required.

Debra Lappin: Great. James Boland in Idaho Falls, do you think you could share your question with us?

Caller: Yes. My question is related to this: Are you obtaining data on the nature of people's anemia, the oxygen in the blood, things of this nature? Because if you look at blood flow, if you don't know anything about the blood that's flowing, I don't know that you learn a whole lot about anything.

Dr. Mackin: Yes. Thank you for bringing that question up. That's a terrific question. I did not spend a lot of time on this, but we're accomplishing that in several different ways. First, we're collecting whole blood samples, so we're actually banking samples so that we can run future analyses; if the question might come up in the future that we did not think about and we need some additional information we'll have those samples that we

can go back to. We're also collecting information on RNA, DNA, APOE genotyping, we're collecting hematology labs, cell lines, and collecting samples to look at telomeres. So in short, yes, we're collecting a lot of that information so that we can not only look at the areas that we have specific hypotheses about, but we can also compare that and draw upon the expertise of other researchers worldwide that might have a different approach, a different way to look at some of these questions, and this way by having these biomarkers banked, we can go back to them, and make them available for these other types of questions. So that was a great question, and I apologize for not being more clear about that initially.

Debra Lappin: That was a wonderful question, James. And I see a follow-on to that from Jen Romnes. The question is this: You had mentioned about sharing data on genetics, so what role will big data play, if any, in the way you are setting up the data-sharing opportunities for worldwide sharing, and have any discoveries that you've seen, even early on, point to specific gene sets that show an increased risk for depression and AD [Alzheimer's disease]?

Dr. Mackin: That's another great question. So this is an area that there's a lot of interest in right now, particularly National Institute of Health, National Institute of Mental Health, is very interested in, how can we really capitalize and maximize the data that we're collecting in all these individual studies that are occurring across the country. The easy answer is, we need to find ways to make our data available to other people, or potentially combine data sets. Now that sounds like something that's very easy to do; unfortunately it's not, it's not that easy to do, but we're making a lot of progress.

The ADNI study, in particular, I think, was really a pioneer in this area. The whole premise of the larger ADNI study started by Dr. Weiner was, in order to advance scientific discovery, we need to have a lot of people looking at this data and we need to standardize our procedures and protocols so that we can collect data from fifty or fifty-five sites across the country. And now, ADNI has kind of moved in to this worldwide model, so there are other countries that are employing the same protocols and procedures so that, again, they can compare their data directly with ADNI data or combine data sets.

We're really hoping to do the same thing. There are barriers to doing that; the approach that we have taken is that all of our data will essentially be filtered down into a common data set. There is a mechanism where researchers can request access to that data and link various aspects of the data; if they're interested in cortical atrophy, or cognition, or genetic data, they can link all of those things together to answer questions that they might have. So that's really one of the things that we're hoping to do.

Now the second part of that question is, are there specific gene sets that we're thinking would be risk factors for depression? That's a longer answer. What we've tried to do, again, with our approach, is: we're going to look at it from both sides. What are the risk factors for depression, and potentially is there different risk for early onset or someone who might have depression throughout their life, as compared to someone who is more likely to develop depression later in life, and then potentially, how does this interact with some of the genetic risks for Alzheimer's disease?

Debra Lappin: Question: Are there antidepressant drugs that would have a greater expectation to improve cognition, and if so, what are those classes? SSRIs? Are there any that are better in terms of classes? And then the opposite question came: Do you believe that there are any classes of antidepressants that could pre-dispose somebody to Alzheimer's? I think I know the answer to that, but I will ask both questions.

Dr. Mackin: Sure. These are great questions. Right now, to answer the first question, are there antidepressants that are better at treating cognitive symptoms? I guess we could further say cognitive symptoms in older adults versus potentially younger adults. This is a very active area of research right now. There haven't been enough studies that we could say definitively that there are specific treatments that improve cognition, or within classes of medications that better improve cognition. What we can say, is that remission of depression is a key feature. I think it's safe to say that the most important feature is, we need to find a treatment that works for the individual. So there's antidepressant treatments, there's also non-pharmacological treatments such as psychotherapy interventions. I would think the most important thing here is that we treat the symptoms of depression successfully, and that's likely to have the best outcome with respect to cognitive function. But it is true that there are number of studies right now, and a number of different pharmaceutical companies that have different types of interventions that are particularly interested in looking at cognition as a potential endpoint for antidepressants. So that data will be coming, or emerging, soon and continue to grow. So we'll be able to better answer that question soon, hopefully.

Debra Lappin: Very interesting.

Dr. Mackin: I didn't address the second part of that question, and that was, are there any antidepressant medications that might pre-dispose someone to a worse course of Alzheimer's disease. Was that the second part of the question?

Debra Lappin: It was, right.

Dr. Mackin: Right now, the answer to that is 'No'. But again, we need to do more research in that area. So, if we looked at all of the studies that were conducted on the potential impact of depression on Alzheimer's disease, relative to a lot of areas, that's a smaller number of studies, but then looking at specific types of treatments, then the number of studies gets even smaller. So this is a really important area for future work, both with respect to medications that might have a negative impact on Alzheimer's progression, as well as a positive impact. So we really need to answer those questions but right now there's not any indication of a specific medication or antidepressant necessarily that would be linked to a worse course of Alzheimer's disease.

Debra Lappin: And I know somebody asked about statins; do you have a comment on whether statins could be a positive or negative player?

Dr. Mackin: That's also a very active area of research. That's not my area of expertise; I think I'll defer that question to maybe some of your future hosts for the calls.

Debra Lappin: Fair enough. Let me go back, then, to an area where you do have a focus, traumatic brain injury. I think a very important question comes from Kathy Blaustein. Head trauma appears to be correlated with the development of depression. Has it been shown to have a role in the later development of Alzheimer's?

Dr. Mackin: Head trauma, or traumatic brain injury, has been shown to be a risk factor for Alzheimer's disease. I think it's important to keep in mind, when we're thinking about risk factors for Alzheimer's disease, the number one risk factor is simply getting older. When we look at what the added role of something like head injuries is, there is an association just like there's an association with depression, but with head injuries a lot can depend on what type of head injury it was, when it happened, and there are a number of researchers that are looking at this question. The ADNI DOD [Department of Defense] study in particular I believe has a focus on looking at the potential role of TBI

[traumatic brain injury] and the progression of Alzheimer's disease. So the short answer again is, yes, there is a potential risk factor, an increased risk, but the biggest risk for Alzheimer's disease is getting older. And because we don't know what causes Alzheimer's disease, untangling some of these other factors can be difficult in terms of what exactly is the increased risk.

Debra Lappin: I have a couple of questions left, but I want to take a minute because we have the ability on this call to ask all the folks who are listening to you, Dr. Mackin, that if they're interested in getting more information on the ADNI Depression Project, you—on the phone—can press 1, and by doing that, we'll share your specific contact information, confidentially, with Dr. Mackin.

So, I have two last comments, and one, I think, has been on many people's minds. Do you think that there are positive effects of online brain training exercises? Luminosity comes to mind, BrainHQ?

Dr. Mackin: Sure. Again, this is a key area that I think the field is becoming very interested in from across several different standpoints. From my own research, I think it is fairly clear that some of the things that we can all do, to promote positive brain function as we get older, are the basics: getting enough sleep, getting enough exercise, eating well, and trying to avoid or prevent depression. Those are things that we do know have a big impact, potentially, on cognitive function. There's been a growing interest in cognitive remediation. So are there things that we can do, brain training exercises that might help with cognition? The jury is still out there. There are a number of studies being conducted to evaluate that; there are a number of different companies that have developed their own brain training exercises. I probably don't have enough time to go through all of those today. It's certainly an active area of research and something that we'll be looking at very closely in the future. One of the advantages, we do have partnerships with several of these companies with the Brain Health Registry as I mentioned before. What we're using for the Brain Health Registry is, we actually have online measures of cognitive function, so we don't have the cognitive remediation or the cognitive training tools on that web site; we're primarily interested in using measures of cognitive function. But as these companies grow and develop, we'll have more data on the effectiveness of specific intervention techniques.

Debra Lappin: As we think about just the large numbers of people who may be affected by late life depression, and you gave some fairly staggering percentages, what is the best way for those on the call to engage the family physician in this conversation, and to ensure that a patient in the family who may have depression gets the early intervention that could make a difference or at least improve cognition?

Dr. Mackin: One of the key things is simply knowing when to get some help. And the short answer for that is, if the individual or family member is concerned about depression, there are a number of different mechanisms that you can employ. So talking with a primary care physician, making an appointment in a psychiatry clinic, a psychologist, there are a number of people that specialize in the treatment of depression but very often simply talking to a primary care physician can be a critical first step. There are a number of different effective treatments for depression; in both younger adults and older adults, the success rates tend to be fairly high, so the challenge is getting someone to treatment. From there, there are a number of different types of treatments to try. They can be antidepressant medications, they can be psychotherapeutic interventions, they could be group interventions, supportive interventions. This can all be tailored to the individual and their interest. So I think the

most important thing is, if there is a concern, let's find a way to have that evaluated and potentially start treatment, and a primary care physician is an excellent starting place.

Debra Lappin: Dr. Mackin, I suspect there are many people on the line who wish you had a clone in their back yard. You are clearly a very talented investigator and clinician, and it's really been a pleasure for UsAgainstAlzheimer's to host your presentation today on Alzheimer's Talks. Know that there are many questions we couldn't get to today, but I want to thank everybody on the line, and I especially want to thank you, Dr. Mackin.

In about one week, we'll have a copy of a recording and a transcript on the UsAgainstAlzheimer's web site, so it will be there for you to share with your friends. I think passed-along readership and viewership is one of the most important assets that UsAgainstAlzheimer's can bring to the community, as we try to spread, in a very open access way, this kind of information. So thank you, Dr. Mackin. I hope you've enjoyed the day, and maybe one last word from you before I talk about our next call.

Dr. Mackin: I just want to thank you and all of your callers. I really appreciate the opportunity to talk with all of you today. This project in particular is the result of a lot of people's work over a lot of years; I should have listed out all of those, but I really appreciate the opportunity to share our work with you, and to talk about depression and Alzheimer's disease, and, hopefully together and through the support of the callers and UsAgainstAlzheimer's, to really work towards finding that shared pathway to discovery and prevention and treatment for Alzheimer's disease. So thank you again.

Debra Lappin: Thank you.

Our next call will be Thursday, September 17, at 2 p.m. Eastern, with Dr. Randy Bateman. He is the Charles F. and Joanne Knight Distinguished Professor of Neurology at Washington University School of Medicine in St. Louis. Dr. Bateman is the Director of what we call the DIAN studies, the Dominantly Inherited Alzheimer Network, and the Trials Unit for that study is launching the first clinical trials in autosomal dominant Alzheimer's disease aimed to prevent the onset of memory impairment and dementia, hoping to use this population to give us great insight into Alzheimer's. Click here if you would like to register for that call.

As always, stay on the line if you'd like to leave us a message or a further question or comment. We really do appreciate any input you wish to give us, thoughts for future calls, areas that you would like us to pursue, and any comments on today's conversation. I think with that, we're adjourned, and again, thank you for joining us. Thank you, Dr. Mackin.