

### Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:

<https://reachmd.com/programs/cme/qad-addressing-challenges-in-alzheimers-disease-from-early-identification-to-new-treatment-considerations/13485/>

Released: 05/19/2022

Time needed to complete: 30 minutes

### ReachMD

www.reachmd.com

info@reachmd.com

(866) 423-7849

---

Q&AD: Addressing Challenges in Alzheimer's Disease, From Early Identification to New Treatment Considerations

### Announcer:

Welcome to CME on ReachMD. This activity entitled "Q&AD: Addressing Challenges in Alzheimer's Disease, From Early Identification to New Treatment Considerations" is provided by Forefront Collaborative. and supported by an educational grant from Biogen. Here is your host, Dr. Jennifer Caudle.

### Dr. Caudle:

Alzheimer's disease, or AD, affects an estimated 6.2 million people in the United States. And by the year 2050, this number is expected to double. It's a progressive disease, often diagnosed after a patient has developed mild dementia and one that inevitably results in a trajectory of diminished cognitive function and eventual death. Until recently, there were no available drugs shown to impact the pathology of the disease. My name is Dr. Jennifer Caudle and I'm your host today. I'm here today with an esteemed faculty panel. First, we have Dr. Alireza Atri, who is the Director of the Banner Sun Health Research Institute in Sun City, Arizona. We also have Dr. Brad Dickerson, who is the Director of the Frontotemporal Disorders Unit at Massachusetts General Hospital and a Professor of Neurology at Harvard Medical School. And we also have Dr. Sharon Sha, who is the Associate Vice-Chair in Clinical Research in the Department of Neurology, the co-director of the Lewy Body Dementia Research Center of Excellence, and a Clinical Associate Professor at Stanford University. Welcome everyone.

You can find all of our disclosures on the activity page.

### Dr. Caudle:

We're here today to examine the case of a patient who was diagnosed early with mild cognitive impairment, or MCI, due to Alzheimer's disease, or AD, prior to dementia. Through this case, we'll delve into the importance of early detection of Alzheimer's disease and how to detect AD early. Further, we'll discuss the pathobiology of AD and how treatments are being developed to target this pathology. And finally, we'll explore the current treatment options and discuss the appropriate use of a treatment that recently received accelerated approval.

As you listen to this podcast, think about the questions you may have for this faculty team. That's why this is a two-part series. At both the midpoint and at the end of this activity, we plan to collect questions we will use to create future education, including the second iteration of this podcast later in 2022, where we will answer some of these questions. Our activities are built around you, so please make sure to submit those questions.

Now, let me turn this over to Dr. Sha. So, Dr. Sha, could you please share your patient case and describe how you came to a diagnosis of MCI due to AD?

### Dr. Sha:

Yes, this is a story of a 67-year-old man, who's retired, former high-level executive. He presented with slowly progressive memory and word-finding difficulties over three years. He remained independent in his daily activities, although it takes him longer to pay his bills and he is more reliant on his calendar for remembering appointments, according to his wife. He has a history of hypertension and takes

antihypertensives for this. His Mini-Mental State Examination score was 27 out of 30, missing three points all in the memory domain. His Clinical Dementia Rating Score was 0.5 and the brain MRI showed subtle hippocampal atrophy.

He enrolled in the IDEAS Study, which is a research study that allowed for him to obtain a florbetapir PET scan, which demonstrated that he had amyloid in his brain. I came up with the diagnosis of mild cognitive impairment due to Alzheimer's disease, because the CDR, the Clinical Dementia Rating Score, suggests that he is able to manage most of his affairs. And that's consistent with a diagnosis of MCI, or mild cognitive impairment, rather than dementia.

Formal cognitive testing was not mentioned but the Mini-Mental State Examination, also known as the MMSE, did demonstrate some impairment in memory. Formal testing to demonstrate impairment in at least one cognitive domain is required for a diagnosis of MCI, along with a cognitive concern about a change from baseline, with preservation of independence and functional abilities. The biomarkers of amyloid plaques as noted by the PET scan and the hippocampal atrophy as seen on the MRI, are supportive of underlying Alzheimer's disease as the pathology. It's important to note that these biomarkers are not often readily available in the clinical setting, however.

**Dr. Caudle:**

Thank you for that. And Dr. Atri, would there have been anything you would have differently to diagnosis this patient?

**Dr. Atri:**

I agree with Dr. Sha. This was a really good work-up. I generally will think about formal neuropsychological evaluation to better establish a baseline and patterns of strengths and limitations on the different domains, especially at the MCI level, that's really, really important. But my approach is similar. I first elicit history from and subjectively from the patient and a care partner, review the symptoms of changes in cognitive behavioral domains, in activities of daily living even, you know, gait and sensorimotor domains, and really behavior in neuropsychiatric domains. I look at the risk factors for cognitive behavioral decline. For example, have they amassed a number of medications and supplements. You know, the medical, social, and family history's going to be really important in this case, developmental history. Then I do a medical and neurological exam and really, importantly, I do a cognitive behavioral exam that includes a standardized brief instrument like, for example, the Montreal Cognitive Assessment Test, the MoCA.

So, really my general approach is first to understand, how much of a change there is, is there really a basis to suspect there's a cognitive behavioral impairment disorder. If so, at what cognitive functional level? Is it at the mild cognitive, impairment stage, where they're essentially independent? Or are they at the mild dementia stage, for example? And then lastly, I try to think about, what kind of syndrome is this? Is, you know, what's primarily involved? Is it memory impairment, prominent, which is an amnesic type? Or is it a non-amnesic type, for example, involving behavior or executive function or language? This pattern probabilistically tells me, kind of, mabs on what may be the underlying cause or causes or contributing factors in the brain. They actually help me also, with symptom management and coming up with a care plan.

And finally, I do try to utilize biomarkers to rule in and rule out different causes, including, doing a first-tier blood work and structural imaging with MRI, if that's something they can do. I assume in this case, the cognitive first-tier lab panel was done, I generally will send the CBC with diff, a Chem 20 with calc, mag, phos, LFTs. I'll check the thyroid, the TSH, and a B12 level, the homocysteine. And I'll also look for maybe an inflammatory or infectious marker, like ESR or CRP, because in older individuals there may be co-existing conditions that may really contribute to cognitive behavioral changes and can be optimized still. And we'll peek out, some cognitive function.

**Dr. Caudle:**

Thank you for that. And now, Dr. Dickerson, Dr. Sha, and Dr. Atri, you know, although it's wonderful that this patient was diagnosed at an early stage, we know that this is often not the case. So, why is it important to intervene early? And do you have any suggestions for how to improve the earlier diagnosis of AD, for example, the use of screening or imaging tools?

**Dr. Atri:**

Yeah, this timely detection is really, really crucial. It allows really earlier on to give psychoeducation about the condition, about the disease, about the care, about expectations, including, you know, mitigating, and contributing factors, prognosis, planning, management strategies. And, you know, to take away bad medicines, you know, put in a care environment that includes behavioral strategies and nonpharmacological interventions and care planning to minimize harm, including, for, you know, financial, considerations. Plan for future needs, and, you know, basically understand what their desires are and how do we fulfill it, in the time that they have. And that may mean, you know, they may exercise more, they may want to participate in clinical trials, they want to establish practical and healthy habits and lifestyles. I really stress sleep, and hydration, and nutrition, and physical activity, and mental, social engagement. And then, you know, really shoring up support systems before existing abilities are lost. Once they're lost, it's hard to get them back.

**Dr. Sha:**

I'll also add that undetected cognitive and behavioral impairment in dementia can result in inefficient and unnecessary care, higher costs, which can then cause harm to both the individuals, the families, and society.

**Dr. Dickerson:**

And I'll just add that concerns of this sort, really just need to be taken seriously as a potential problem and evaluated. Because, too often, they may be dismissed as normal aging or stress or attributed to depression and partly for this reason, the American Academy of Neurology developed Mild Cognitive Impairment Guidelines that were published a few years ago, that said that there are number of important elements to consider in the assessment of a patient with concerns about memory impairment. And some of those are the need to use validated instruments to perform an initial assessment of cognition, mood, behavior, and function, as was mentioned by both of my colleagues.

The fact that it's really critical to involve an informant in most cases, to obtain an independent perspective on the patient's symptoms and daily life. Many patients really are not fully aware of the problems that they're experiencing. And most patients, like this should really undergo an MRI to get a good quality set of images of the organ of concern. And potentially, as Dr. Atri mentioned, a referral to a neuropsychologist, especially when a patient is at a mild stage, and we really want to try to find out what some of the patient's cognitive strengths are that could be marshalled to help compensate for some of the difficulties the person is having.

And then, a general medical work-up is always important to consider, depending on what the patient's background, medical conditions, and psychiatric conditions have been.

**Dr. Caudle:**

So, Dr. Atri, we know that the pathophysiological process of Alzheimer's disease begins years before clinical symptoms are evident. How is beta-amyloid thought to contribute to the development of Alzheimer's disease?

**Dr. Atri:**

Well, Alzheimer's disease, pathobiologically is defined by accumulation of beta-amyloid plaques and neurofibrillary tangles in the brain. One can think of this as a very, very complex disease. This is not the only two things that go wrong in the brain, over this process of 20 or 30 years or more, before symptoms start. I think of it as, amyloid beta, 42, being toxic both in soluble and also potentially in plaque forms. And Alzheimer's disease being an amyloid-induced, tauopathy in some ways. So, the analogy I have is, toxic kindling in the brain is started by these sticky and toxic amyloid proteins, and, ultimately, they start a fire of inflammation, and phosphorylation of tau, which ultimately leads to a number of things that go awry inside and outside neurons in the brain, including breakdown and failure of energy systems in the brain, including toxic protein.

And ultimately leads to synaptic damage and neurodegeneration. And that's really the final common pathway, that synaptic damage and neurodegeneration that leads to kind of behavioral changes. But, you know, it's a long pathway and in between there's vulnerabilities and resilience factors that could work in. But again, you know, amyloid is central, and necessary, maybe, but not sufficient.

**Dr. Caudle:**

Okay. And Dr. Dickerson, how is tau thought to also contribute to the development of Alzheimer's disease?

**Dr. Dickerson:**

Well, as Dr. Atri said, you really need both the amyloid-based neuritic plaques and the tau-related neurofibrillary tangles to have a pathological diagnosis of the disease. And now we're able to measure these proteinopathies using biomarkers in living people. So, it's really remarkable that we can see these things in living people now, and we don't have to wait for an autopsy in order to confirm it.

So, as Dr. Atri mentioned, Alzheimer's disease is not just amyloid plaques, they are always present when a person has Alzheimer's disease, but if you just have plaques, you're considered at this point to probably just be in the earliest stages of what's called cerebral amyloidosis. At some point, tau is accumulated and spreads throughout the temporal lobes, usually, and starts to affect the function and ultimately the structure of the brain, as can be measured by fluorodeoxyglucose-PET, which measures the glucose metabolism of the brain and MRI. And so, by the time, a patient shows hypometabolism and/or atrophy shrinkage, if they have Alzheimer's disease, it's usually because the tau has aggregated as tangles in those areas that are dysfunctional within the brain. And that's really thought to be one of the proximate causes of that neurodegeneration.

So, you really need amyloid and tau, and ultimately the neurodegeneration is what leads to a patient having symptoms.

**Dr. Caudle:**

And Dr. Sha, how are amyloid and tau, both being targeted by treatments in development?

**Dr. Sha:**

There's a lot of headway being made with clinical trials, testing, treatments for both amyloid and tau individually, with protein-specific

targets. There are monoclonal antibodies targeting amyloid that are currently in advanced stages in investigation, including donanemab, lecanemab, aducanumab, and gantenerumab. Both donanemab and lecanemab have received break-through status from the FDA. And aducanumab has recently, received accelerated approval by the FDA.

I'll start talking about donanemab briefly. The phase 2 trial, which was published last year, had enrolled 257 patients with early Alzheimer's disease and the primary outcome was a change in the Integrated Alzheimer's Disease Rating Scale, also known as the IADRS, at 76 weeks compared with placebo group. This primary outcome was met, but secondary outcomes including the CDR–Sum of Boxes, ADAS-Cog 13, ADCS-iADLS, and MMSE, which are all measures of cognitive and functional independence, were not significant.

There's a clear reduction in amyloid plaque burden as demonstrated by florbetapir PET scan, which demonstrated target engagement, meaning that the drug reached the target and removed amyloid. Other biomarker outcomes did not demonstrate a difference between groups such as the tau load, as assessed by flortaucipir PET and hippocampal volume.

The serious adverse events were not different between the two groups, but the incidence of ARIA, also known as amyloid-related imaging abnormality, and there are two forms of this. ARIA-E for edema and ARIA-H for hemorrhage. And these are demonstrated in the brain. The incidence of ARIA-E was higher in the treatment group, 27% versus 0.8%. And symptomatic ARIA-E was 6% in all donanemab treated patients, which was 22% of the total ARIA-E. This phase 2 data is promising, namely demonstrating target engagement, and meeting the primary endpoint. However, it was a small study and not designed for efficacy. The phase 3 trial, TRAILBLAZER-ALZ 3 is ongoing with the goal of enrolling 3,300 participants.

Lecanemab is another in monoclonal antibody targeting amyloid. And the phase 2 trial published last year included 854 patients with mild Alzheimer's disease. They reported that the high dose, 10 milligram per kilogram biweekly dose group had showed a 64% probability, to be better than placebo by 25%, on their primary composite clinical outcome measure, the ADCOMS. But it missed the primary outcome, which needed an 80% threshold. The high-dose group showed reduced brain amyloid, again demonstrating target engagement. The CSF biomarkers were supportive of a treatment effect. Lecanemab was also well tolerated with a 9.9% incidence of ARIA in the group receiving the 10 milligram per kilogram biweekly dose.

The main concern about this study was that the study did not randomize ApoE4 positive participants, which was 70% of the study population to that high-dose 10 milligram per kilogram biweekly dose. And those who were on it less than six months were discontinued. This change causes an imbalance in treatment groups based on the genetic status and limits any findings from this trial to more general population.

The CLARITY Trial, a phase 3 trial, to include more than 1,700 patients is ongoing now.

And then finally, aducanumab was granted accelerated approval by the FDA in June 2021. It was granted accelerated approval based on the reduction the beta-amyloid and is indicated for use with mild cognitive impairment due to Alzheimer's disease, or mild dementia due to Alzheimer's disease.

There were two phase 3 trials that enrolled over 3,000 participants. One study had demonstrated a difference between the high-dose treatment group versus placebo on the primary outcome, the CDR–Sum of Boxes. However, the second study did not show this change. Both studies demonstrated target engagement with reduction in the amyloid PET SUVR. However, the differences in results for the primary endpoint, the Mini-Mental State Examination, the ADAS-Cog 13 and the ADCS-ADL MCI, between the two studies led to controversy about this approval. The studies were also halted prior to completion, leading to incomplete data.

The main concern about side effect is also ARIA. Overall, there's 40% ARIA for patients who received, aducanumab. ARIA-E, in the high-dose 10 mg per kilogram dose, was 35% overall and was more likely to occur in ApoE4 carriers, 42%, versus noncarriers, which occurred in 20%. Most of the ARIA-E developed within the first eight doses and a majority were asymptomatic, 74% of patients. And majority of them also resolved, 91% within 20 weeks of dosing. ARIA-H, which also stands for hemorrhage, 19% had microhemorrhage and 15% had superficial siderosis.

Another study to confirm these findings and mandated by the accelerated approval is planned, called ENVISION.

Tau therapies are also in the early stages, using monoclonal antibodies as well. And data from these trials may provide insight into the benefits of treating these pathologies separately. However, many of us in the field believe that we may ultimately need to treat both pathologies with combination therapy, or even a multi-pronged approach, addressing inflammation, and amyloid, and tau. Further research to testing both these therapies will help answer these questions.

**Dr. Caudle:**

And now that we have reached the midpoint of this podcast, this is a gentle reminder to please submit a question for the faculty who will

respond in the second part of the series later this year.

Now let's return to the patient case. As a reminder, we're currently discussing the case of a 67-year-old male with mild cognitive impairment due to Alzheimer's disease. He had a score of 27 out of 30 on the MMSE, a CDR of 0.5, and an MRI of his brain showed subtle hippocampal atrophy.

Dr. Sha, could you please describe what were the treatment options for this patient and the rationale behind your treatment decision?

**Dr. Sha:**

Yes, cholinesterase inhibitors are really the mainstay of treatment, though mainly approved for patients who have dementia due to Alzheimer's disease rather than mild cognitive impairment. It can be used off-label for the use of mild cognitive impairment. There's no clear evidence that cholinesterase inhibitors are beneficial or delay decline in memory in mild cognitive impairment patients as noted in dementia patients due Alzheimer's disease, that many prescribers offer this treatment. The American Academy of Neurology updated guideline from 2018 suggests discussing this lack of evidence with patients if you are to prescribe it, but also recommend discussing exercise. The main side effects are procholinergic if you do give this drug, which are often gastrointestinal upset, rare bradycardia, urinary frequency, among others. Exercise is important, and we discussed that with this patient.

At the time, enrolling in a clinical trial is my only other choice for a medication treatment, besides the cholinesterase inhibitors that we talked about. He was enrolled in a clinical trial and received aducanumab, which as we mentioned early, has now received accelerated approval by the FDA.

**Dr. Caudle:**

And Dr. Atri and Dr. Dickerson, now that aducanumab has received accelerated approval, what would be some arguments for and against the use of aducanumab, for a patient like the one in this case, and how would you resolve these arguments? Dr. Atri, why don't you start with the supporting argument.

**Dr. Atri:**

Well, I would say, you know, autonomy and respect for patients to be able to make informed decisions, and us, you know, to help them in a patient-centered shared decision-making paradigm, if this one would be appropriate for them. So, aducanumab is available, it's an FDA accelerated approved drug. It was based on not definitive proof of efficacy, but by removing amyloid from the brain, with signals from one study that there may be clinical benefits. And that, along with the class of drugs that Dr. Sha reviewed, suggests that there may be 20, 30, 40% possibility for some groups to benefit with amyloid removal. But I would be really, really upfront. It's not a cure. None of these drugs are cures, you know. They are meant to slow down, at best, the progression of the disease in the brain and give people an opportunity. But what it comes down to is first, are they the appropriate candidate?

So, there's the FDA level, label, and there's also the Cummings et al Appropriate Use Criteria for aducanumab, which has just recently been updated. And, you know, the patient fits the right age, as far as being early enough in the condition clinically, so MCI due to AD or mild dementia. We do want to make sure, right, that individuals actually have amyloid in their brain so there is proof that they have, as Dr. Dickerson mentioned, cerebral amyloidosis, along with this, counter manifestation, so amyloid PET or CSF findings that are consistent with AD.

And then, really what I think what it's important is to make sure that also they are not at much higher risk. So, not on anticoagulants, they don't have severe, white matter disease in their brain, they don't have microhemorrhages at baseline, you know, many of them. And, if all those things fit, then, this option can be presented to patients for us to respect their autonomy, to make that decision while we guide them.

So, I think that we do have to be humble and that we're not all-knowing about who may respond and benefit. And what may be of value to them clinically and not deny them this opportunity. Again, if they can make this really informed, decision-making about the burdens, the risks, the costs, to them it's an infusion, there's coverage issues, ARIA has to be monitored. And, on the other hand, many are facing the reality of living with an incurable, relentlessly progressive neurodegenerative disease. And for them, as a clinician, if you have the proficiency and resources to support somebody through that, then I think it would be appropriate to offer it to them. And I think it would be a small slice of individuals with MCI due to AD but that's where I would, sort of, stop as far as thinking about who's appropriate and helping them decide.

**Dr. Dickerson:**

I couldn't have said it better, I think, we've been waiting our whole careers to be in the position of being able to tell someone that we diagnosed with the condition that Dr. Sha presented in her case, "we have a treatment that can help slow down the progression of this inevitable decline that you're facing". That's what we've been waiting for. I think, you know, we will all jump at the opportunity to give



people a treatment like that, even if does come with some challenges logistically, risks, and costs.

I think the problem is that when we really sit down and try to explain to a patient, many of whom at this stage are quite capable of engaging in a sophisticated conversation about risks and benefits, that the efficacy data just don't show a robust and reproducible benefit in terms of slowing the progression of the disease, clinically. I think that we all hope that the reduction of amyloid in the ways that were robustly and reproducibly demonstrated will lead to that clinical benefit if people are given the treatment for longer. But we just don't have the evidence for that yet.

So, I think if this were just a pill that people took once a day, if they didn't have to be monitored for the ARIA and the related potentially significant side effects that this can cause, and if the costs were reasonable and paid for by insurers, most of us would probably be willing to take the chance. But the biggest problem is that Medicare came out with the National Coverage Determination recently that this medication will only be covered if a patient is participating in an NIH or FDA-approved clinical trial, and in which case they will also pay for the amyloid PET scan, which is not currently something that's paid for outside of research in most settings.

So, that's a major problem. People aren't going to be able to access it because of the fact that they would have to pay out of pocket for all these costs. And the costs themselves have been a major concern with Biogen reducing its initial projected \$56,000 a year cost down to \$28,000 a year. But many cost-benefit analyses having been run since then that have suggested that even that is too high for a drug with the, you know, questionable level of efficacy and risks that are involved.

**Dr. Caudle:**

And Dr. Sha, can you please provide us an update on this patient? Did he benefit from treatment?

**Dr. Sha:**

It's a wonderful question. You know, as we mentioned earlier, aducanumab is not expected to reverse or improve cognitive impairment, so how did we know if he'd benefit? It is supposed to delay decline. He was already a high-functioning individual, which often means that there would be a slow progression, anyway.

After three years of being on treatment, functionally, he remained largely independent in his daily life with a CDR-Sum of Boxes - or CDR Global Score of 0.5, which was the same at the time of enrollment into this study. Despite developing ARIA six times, he was stable. Was just this individual feeling like he was relatively stable? Could this be beneficial for him. This might be, we just don't know. In total, he received 31 infusions with a cumulative dose of 124 milligrams per kilograms over 44 months, until the trial was halted.

I should mention that he was frequently monitored because he was in a clinical trial. And when you're in a clinical trial, there's often extra safety monitoring. And as mentioned earlier, frequent MRI monitoring for assessment of ARIA is important, which is not often the case, and present in clinical settings.

**Dr. Caudle:**

And thank you for sharing this patient case, Dr. Sha. I'm sure hearing your experience has been very helpful for our learners.

And now as we wrap up this podcast, Dr. Atri, what should our listeners take away from this patient case?

**Dr. Atri:**

Well, I would say that kudos to Dr. Sha and her team for making the diagnosis early in this patient, that allowed him to have the opportunity to make an informed decision to go into a trial. While the experience of this patient with recurrent ARIA after treatment with aducanumab is quite uncommon, as far as, you know, six times, it serves to illustrate some major points. Recurrent ARIA is possible, it requires, vigilance, for clinical changes in symptoms as well as close MRI safety monitoring, by individuals who are proficient. And as you know, it requires baseline MRIs and then, based on the label and also appropriate use criteria, multiple MRIs afterwards, during titration of dose. And it can include dose suspension or termination if warranted.

And again, the Appropriate Use Criteria, has a number of principles regarding management, regarding when to do MRIs, when to stop, when to hold, when to suspend, how to deal with potential side effects. But ultimately, it goes along with having an informed conversations with patients and families regarding the risks and benefits of treatments and allowing them to be in charge of their own fate with us being there, giving them guidance.

And for some people, the hope is very, very important and I'm actually very hopeful about our field, because even though drugs like this, the second-generation mabs aren't going to be used the same way 10 or 15 years from now. They are the tip of the spear and as Dr. Dickerson said, we have biomarkers now. So, we will learn, just like oncology, how to personalize in the coming years, how to use to the biomarkers to see who to give the drugs to, how much, how to tweak the doses, how to manage the safety. So, I think it is a hopeful time in our field.

**Dr. Caudle:**

Thank you so much, Dr. Atri. Now, this concludes our discussion. And I'd like to thank Dr. Atri, Dr. Dickerson, and Dr. Sha for joining me today for this important discussion. I know we're all going to walk away from this podcast with an improved understanding of the pathobiology and early detection of Alzheimer's disease as well as the appropriate use of anti-amyloid monoclonal antibody treatments.

I just want to remind our listeners to remember to enter your questions into the polling question to follow. We will be answering as many questions as we can in a future podcast. Thank you for listening and have a great rest of your day.

To receive your free CME credit or to download this activity, go to [ReachMD.com/CME](https://ReachMD.com/CME). This is CME on ReachMD. Be part of the knowledge.

**Announcer:**

This has been CME on ReachMD. This activity was provided by Forefront Collaborative and supported by an educational grant from Biogen. To claim your credit, please visit [reachmd.com/cme](https://reachmd.com/cme). Thank you for listening.