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CME/CE Information

CME/CE Released: 06/19/2012; Valid for credit through 06/19/2013

Target Audience

This activity is intended for psychiatrists, primary care physicians, and nurses.

Goal

The goal of this activity is to impart a greater understanding of the neurobiology of depression and how it influences treatment decisions.

Learning Objectives

Upon completion of this activity, participants will be able to:

- Discuss the current treatment landscape in depression
- Identify biological and genetic pathways that play a role in depression, including neuroreceptors and hormones
- Critically evaluate emerging data on diagnostic tools and treatments relating to the biology of depression

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An Update on the Neurobiological Understanding of Depression CME/CE

J. Craig Nelson, MD; Roy H. Perlis, MD, MSc; Charles Raison, MD; Michael E. Thase, MD

CME/CE Released: 06/19/2012; Valid for credit through 06/19/2013

Slide 1.

J. Craig Nelson, MD: Hello, I am Craig Nelson. I am the Leon J. Epstein Professor of Psychiatry and director of Geriatric Psychiatry at the University of California, San Francisco. I would like to welcome you to this program titled "An Update on the Neurobiological Understanding of Depression."

Slide 2.

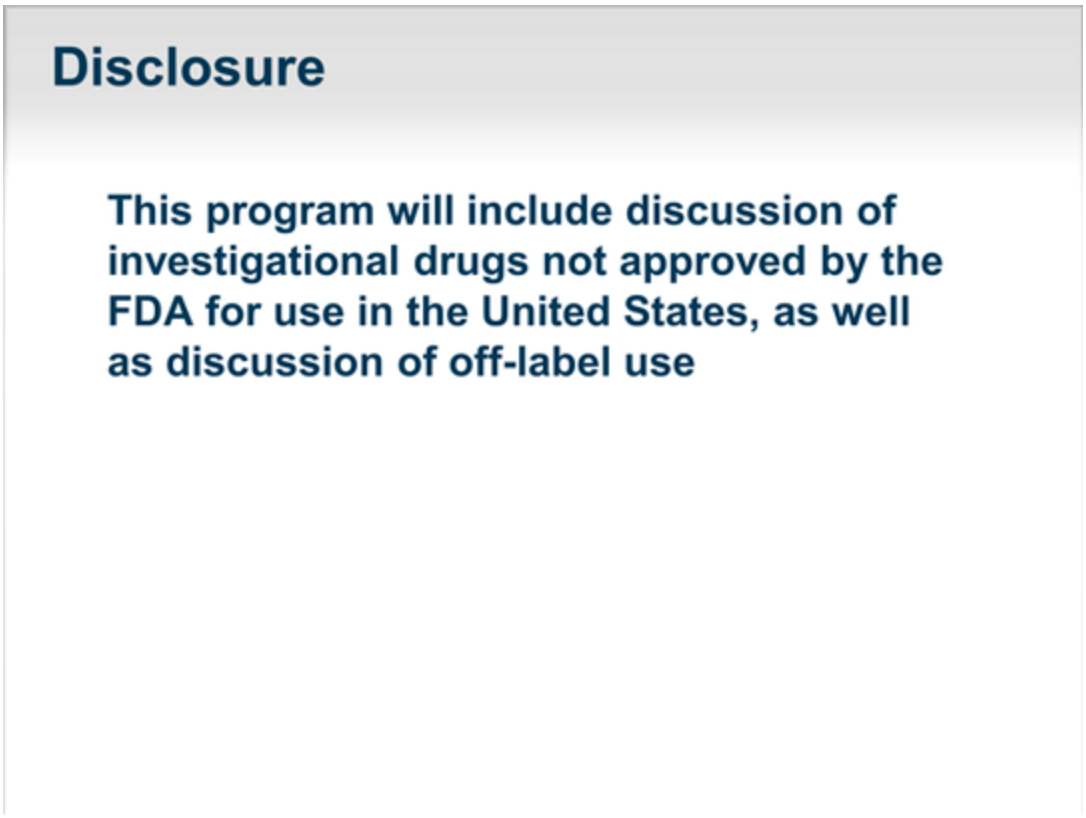
Joining me today is Roy Perlis, director of the Center for Experimental Drugs and Diagnostics, Department of Psychiatry, Massachusetts General Hospital, and associate professor of psychiatry, Harvard Medical School. Welcome.

Roy Perlis, MD: Good morning.

Dr Nelson: Also joining us today areCharles Raison, Barry and Janet Lang Associate Professor of Integrative Mental Health, University of Arizona, Tucson, Arizona; and Michael Thase, professor of psychiatry and director of the Mood and Anxiety Section, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania. Welcome, all of you.

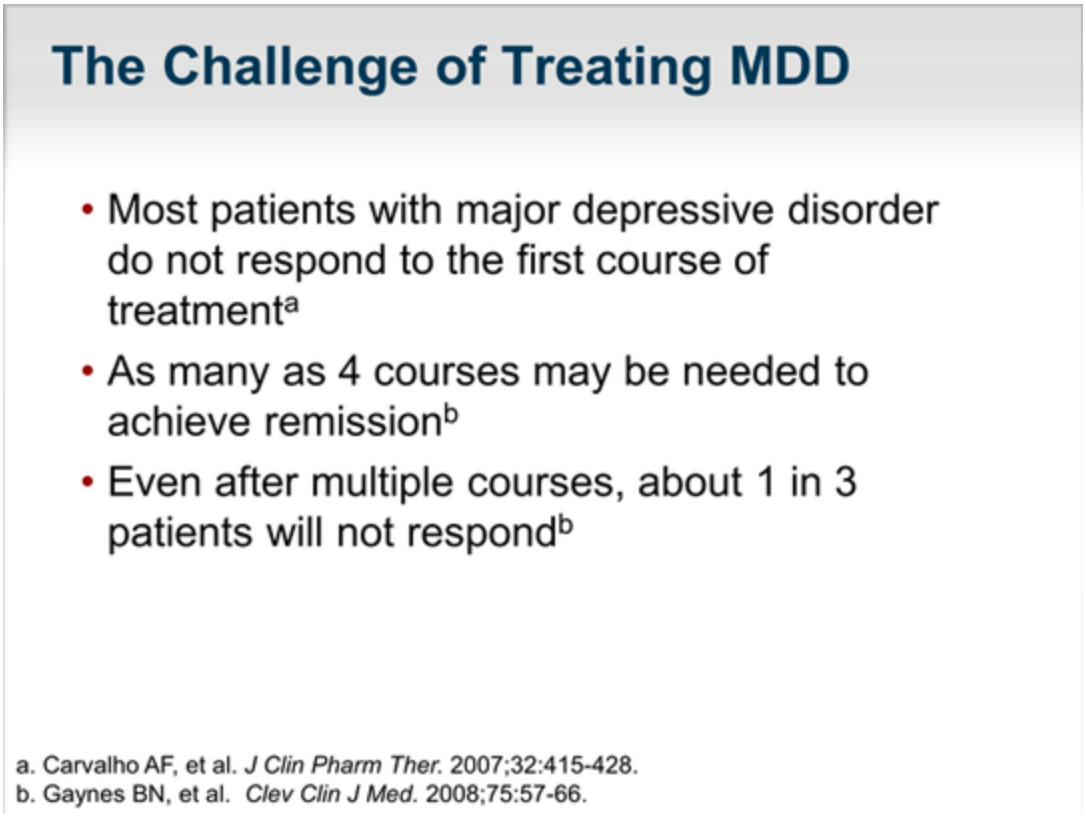
Slide 3.

The goals of this program are to discuss the current treatment landscape in depression, identify biological pathways that may play a role in depression, and evaluate emerging data on diagnostic tools and treatments relating to the biology of depression. At times during this discussion we will pause to ask a few polling questions. Your answers will help us develop future educational programs.



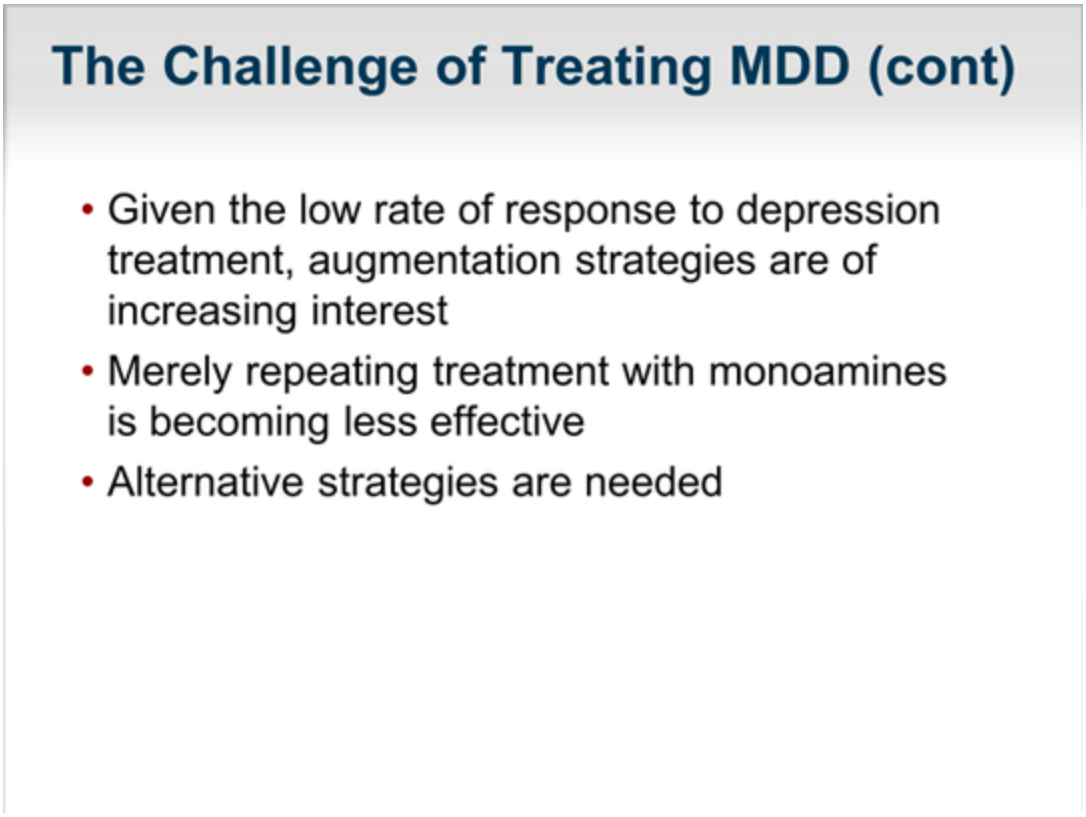
Slide 4.

Before we begin, I would like to note that this program includes discussion of investigational drugs not approved by the US Food and Drug Administration (FDA) for use in the United States, as well as discussion of off-label use.



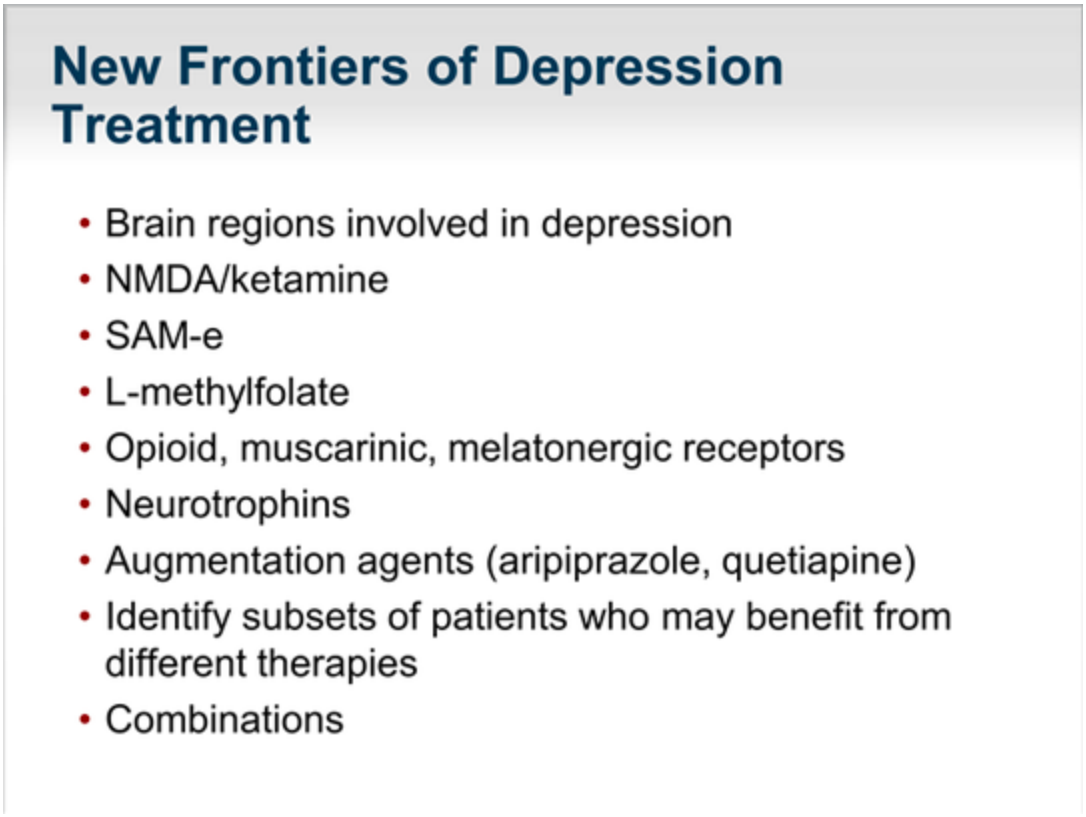
Slide 5.

As clinicians, we face the challenge of providing effective treatments for our patients with major depressive disorder. At least half of these patients do not respond to the first course of treatment; two-thirds fail to achieve remission during initial treatment. It may take as many as 4 courses to achieve remission, and even then it is still the case that 1 in 3 patients will not respond. We need to expand our understanding of the underlying physiology of depression. Today we will look at just a few of the many intriguing avenues of research that may guide us to new treatment approaches. Michael, I would like to ask you if you could give us a 20,000-foot view of some of the emerging data so that we might have a better understanding of the neurobiology of treatment-resistant depression.



Slide 6.

Michael Thase, MD: Sure, Craig. When someone is not responding to first-line antidepressants or even first- and second-line antidepressants, you know that they have not benefitted from the placebo-expectancy effect and they have likely not benefitted from the specific effect of the antidepressants. This is why in the STAR*D study we observed that there was a decreasing chance of benefit with each successive trial -- that we were exhausting the mechanisms, if you will.[1] In the future, we will look for depressions that may be less involved with dysfunction of monoamines or at least less likely to benefit from interventions that target serotonin and norepinephrine reuptake.



Slide 7.

There are all sorts of possibilities. It is true on one hand that there have not been new blockbuster or breakthrough antidepressant treatments introduced in the last decade, but it would not be true to say that there are not candidates or possibilities. You just start looking for regional areas of dysfunction or evidence of dysfunction within networks of brain function. One interesting area of research is looking for almost immediate changes in cognitive-affective reactivity that can be observed when antidepressants are effective and looking for individuals for whom those changes are not evident. Those may be people for whom different targets are warranted.

The most exciting recent experimental therapeutic development has been the rapid and dramatic antidepressant effects for ketamine, suggesting that glutamatergic targets for novel antidepressant treatments are an area worth exploring. There is no evidence that you need the psychomimetic or dissociative effects of ketamine to see the mood benefits. It is very possible that those effects can be uncoupled, and that safer, more tolerable antidepressants that work completely differently are on the horizon. There are nutraceuticals and other nonconventional antidepressant treatment; s-adenosylmethionine (SAM-e) and L-methylfolate are examples of this. Within more conventional avenues of drug development, worthwhile mechanisms that have not yet been well developed include medications that interact through opioid or muscarinic or even nicotinergic targets. Lastly, that you can add second-generation antipsychotic medicines to ineffective selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) suggests that, at least for a subset of patients, other pathways are important and can result in remission.

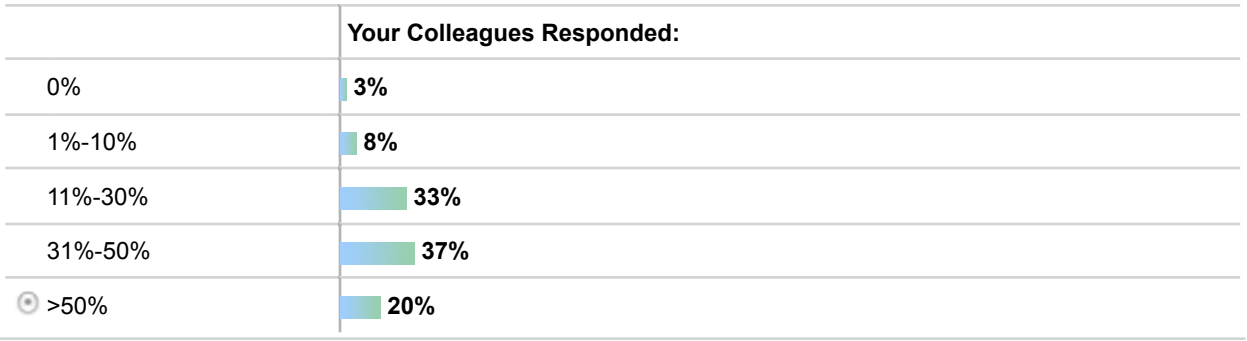
Dr Nelson: Michael, do you have an opinion on whether we will identify small groups of

patients who will respond to specific novel treatments or are we more likely to use combinations of drugs across a broader array of patients?

Dr Thase: We are at the end of the line in developing blockbuster medicines that will treat large groups of patients. It may not be useful to make an SSRI or SNRI that is better than what we currently have, and there may be room for a triple reuptake inhibitor, but even then there will be approximately 1 in 3 or even slightly more patients who will not benefit. Until we can identify specific subsets of patients who may uniquely and powerfully benefit from a novel treatment, we will be using various combinations of medications. I look forward to the day when we can identify a selected deficit or target and pick a specific medication for a specific patient.

Dr Nelson: Thank you, Michael. Now please take a moment to answer our first polling question.

In your experience, what percentage of the patients you treat for major depressive disorder do not respond to the first course of treatment you prescribe?



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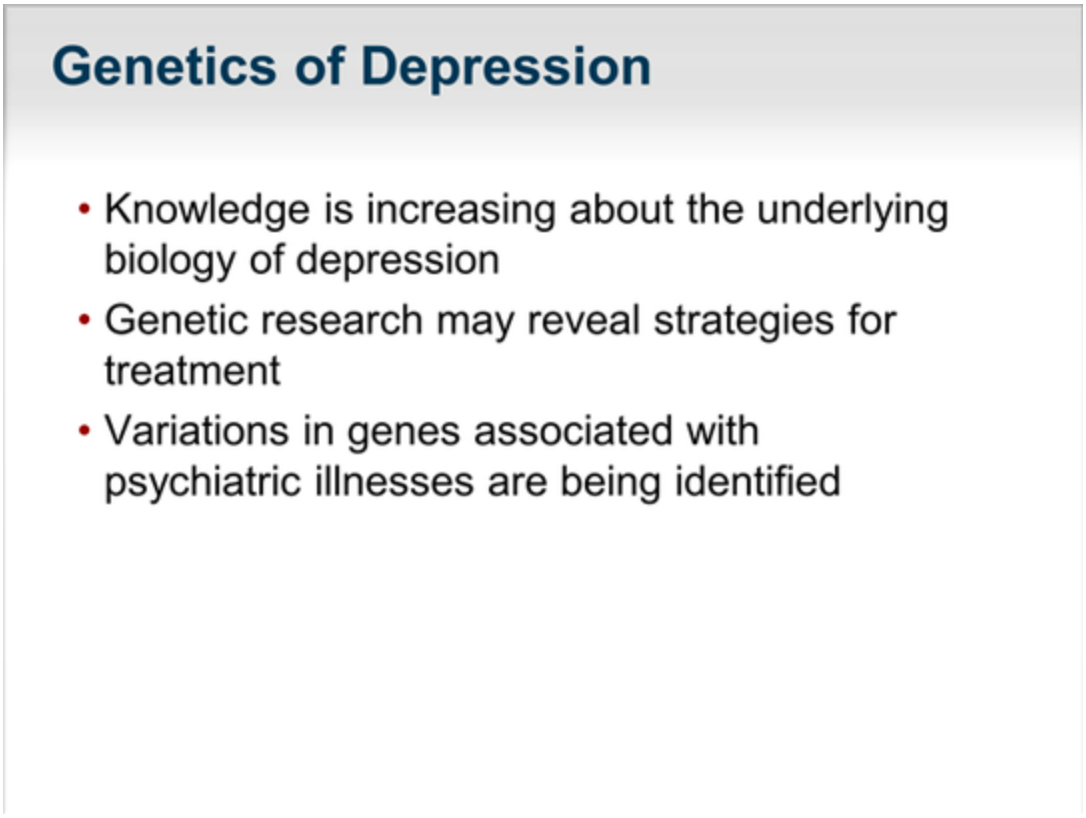
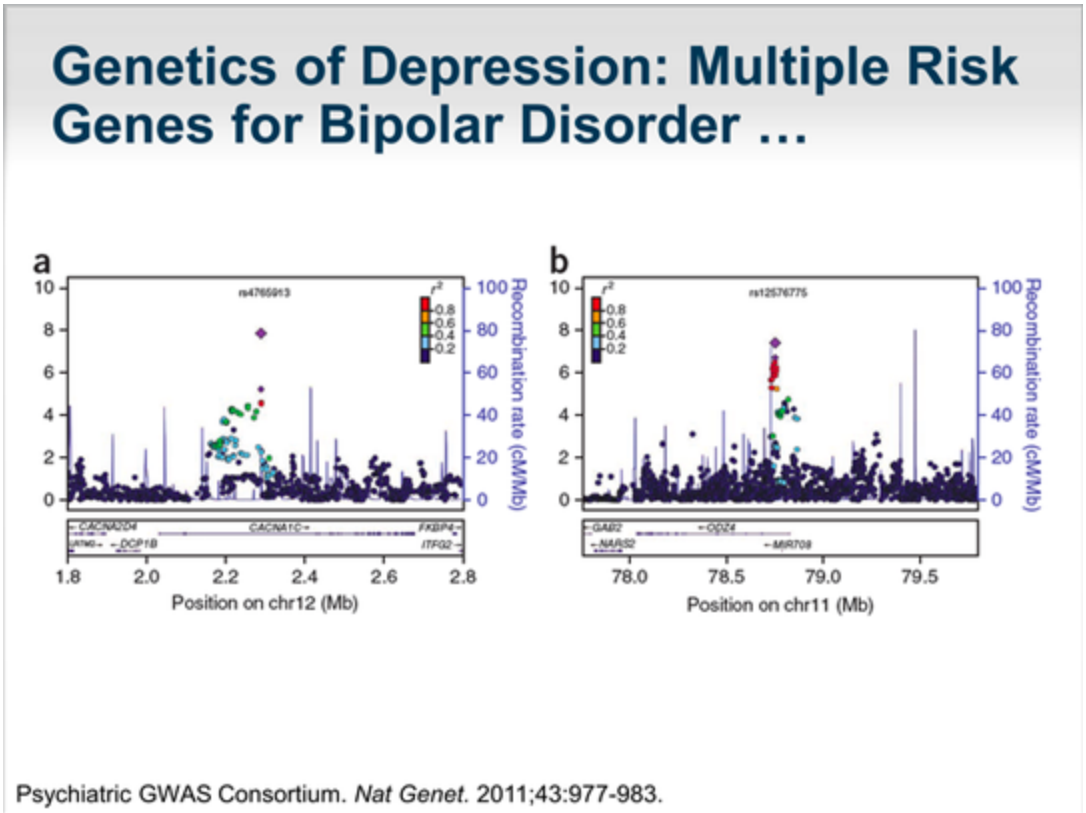


Slide 8.

Dr Perlis: The reason to think about the genetics in terms of depression and antidepressant response is that if we want to stop inventing the same monoaminergic antidepressants over and over again, we need to know more fundamental biology. That is why many of us are

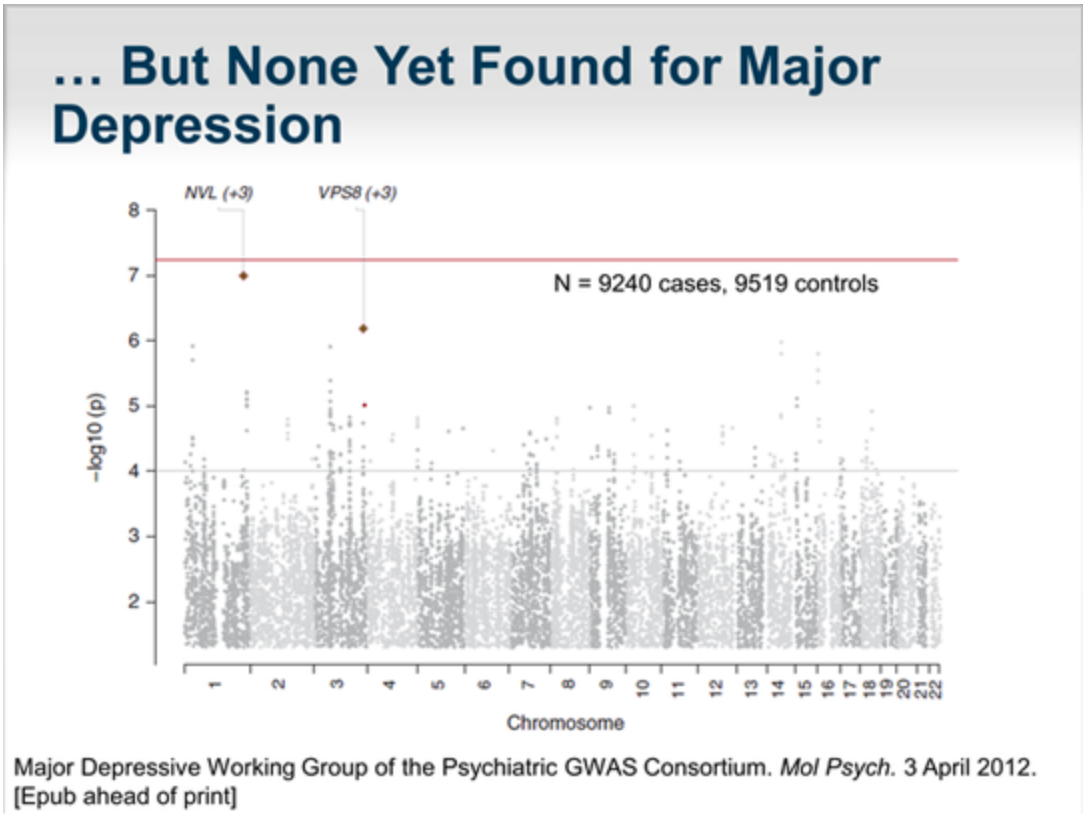
excited about ketamine. It is not just a potential new therapeutic strategy but it opens up the biology tied to NMDA receptors and downstream signaling mechanisms. Genetics can play a similar role in the sense that, as we start to identify genes associated with psychiatric illness, it will, we hope, point us to some new biology that we can target with our treatments. The last 2 to 3 years have been exciting because we have finally started to identify common variations in genes associated with psychiatric illness -- for example, schizophrenia and bipolar disorder.

Last fall there were 2 important papers, one for schizophrenia and one for bipolar disorder, which took our count for genes with common variations that increase risk for these diseases to approximately 6 to 7 for schizophrenia and 4 to 5 for bipolar disorder. As we accumulate knowledge, a single gene by itself may not point us toward a new drug, but if these genes were found to be part of pathways, it would give us a way to think about new therapeutics.



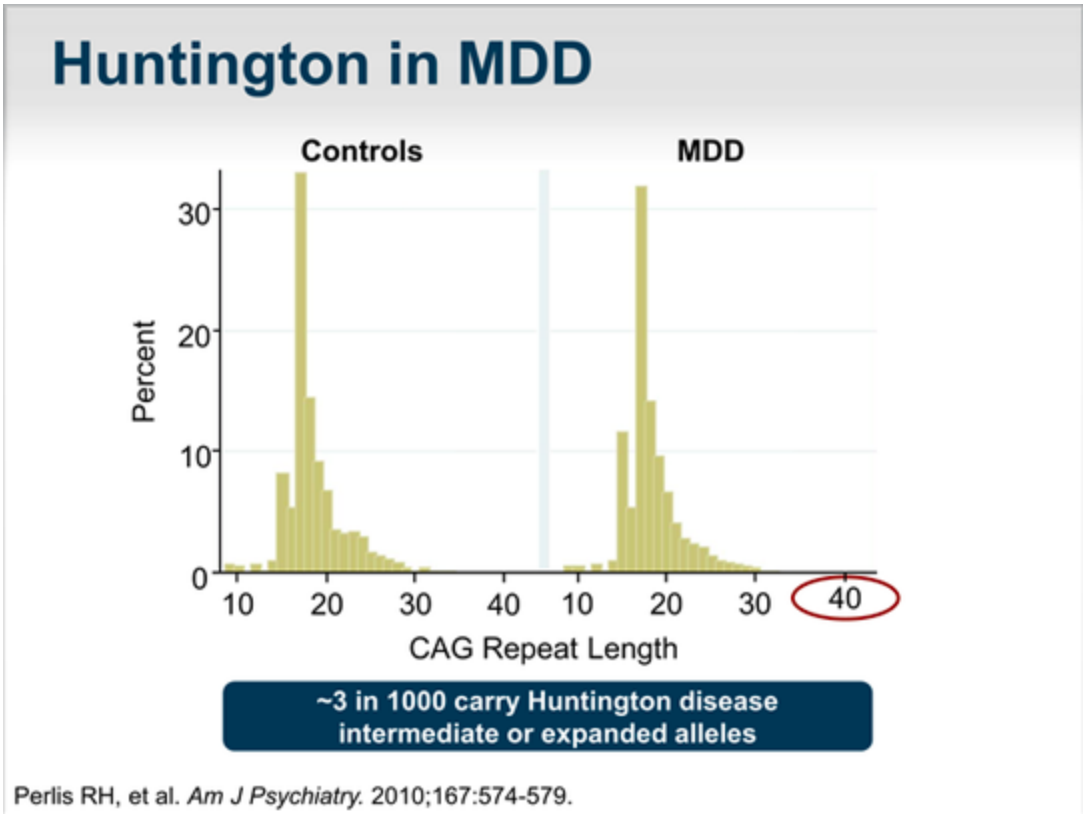
Slide 9.

One example from the recent bipolar literature is that 1 of the bipolar risk genes is actually a subunit of L-type calcium channels. There is a long history of using calcium channel blockers in bipolar and sometimes other mood disorders. By identifying that gene and convincingly demonstrating an association with bipolar disorder, we can now say, "Okay, let's start to think about other drugs that modulate calcium."



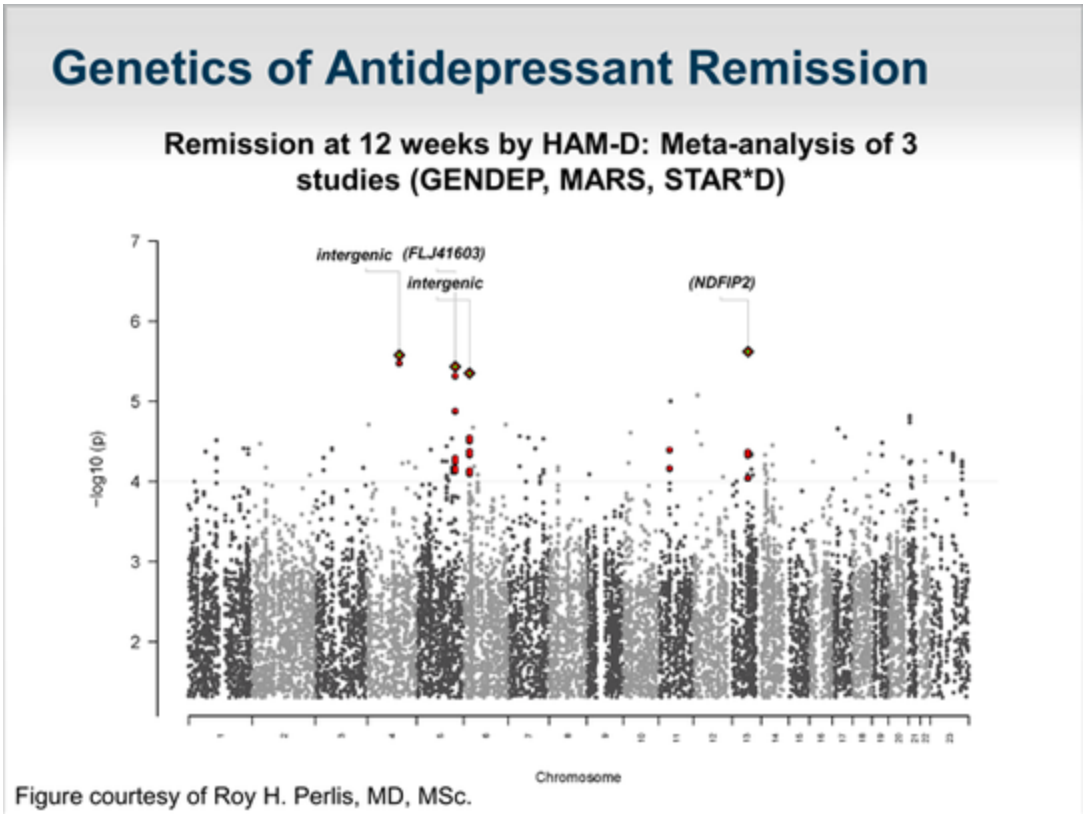
Slide 10.

In depression we have yet to convincingly identify genes that confer risk. A paper in the journal *Molecular Psychiatry* is about to be published that reports the results of a large consortium of study sites that pooled their depression data, looked across the genome, and failed to find a single locus, region, or gene that convincingly increases risk of depression. There are many intriguing candidates but nothing definitive, and there are many reasons why that might be. It may just be, as with other illnesses, that we do not have enough samples yet; we have not studied enough people. You would think 9000 patients and 9000 control individuals would be enough, but not necessarily. It may be that because depression is so heterogeneous, with many different presentations, we must look deeper.



Slide 11.

A few years ago, my group was involved in a study that showed this heterogeneity. We asked, are there some people who present for depression studies who actually carry risk alleles for Huntington disease, since we know that for a subset of people with Huntington, they can present with mood symptoms well before they develop the motor symptoms. We found a small but notable number of individuals -- between 1 and 3 in 1000 when we looked across several cohorts -- who had Huntington risk alleles. Does it mean they all have Huntington disease? Absolutely not, but does it mean that we may start to identify these small subgroups of patients with depression who might require specific kinds of treatments or at least point us to specific treatments. That is the hope.



Slide 12.

The figure on screen is the result of a consortium of sites in the United States, United Kingdom, Germany, and elsewhere in Europe, and we failed to identify any genes that convincingly predict antidepressant response across the genome. What we did find was evidence that across the genome there is some consistency between cohorts. So there are signals. We just have not succeeded in finding the genes yet. This is a work in progress, but it may get us a little closer to understanding the biology of depression, which will help us identify novel therapeutics.

Dr Nelson: Roy, is it fair to say that seeking genes associated with treatment response is still a research tool, that it is limited to advancing our knowledge about the biology of depression, and not about clinical tests for patients at this point?

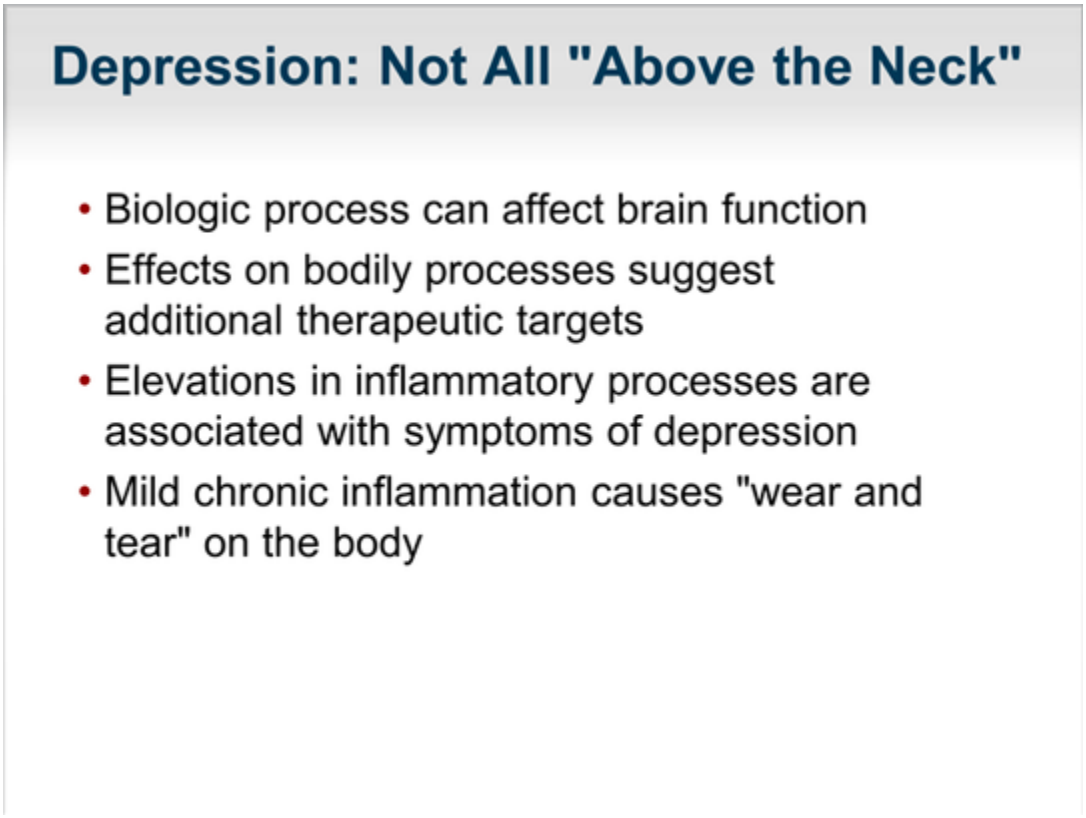
Dr Perlis: It is very much a work in progress. One of the few areas where genetics might inform treatment today is that we know some variation exists in how people metabolize specific psychotropic drugs. So P450 genes like *2D6* and *2C19* for specific treatments can influence someone's degree of response. That is 1 area to pay attention to, where you may see an early transition from genetics to clinical practice. Otherwise, in looking for truly novel targets, we have a way to go.

Dr Nelson: Here is our second polling question.

In your experience, how many courses of treatment are typically needed to achieve remission in your patients with MDD?

	Your Colleagues Responded:
1	3%
2	29%
3	43%
>3	26%

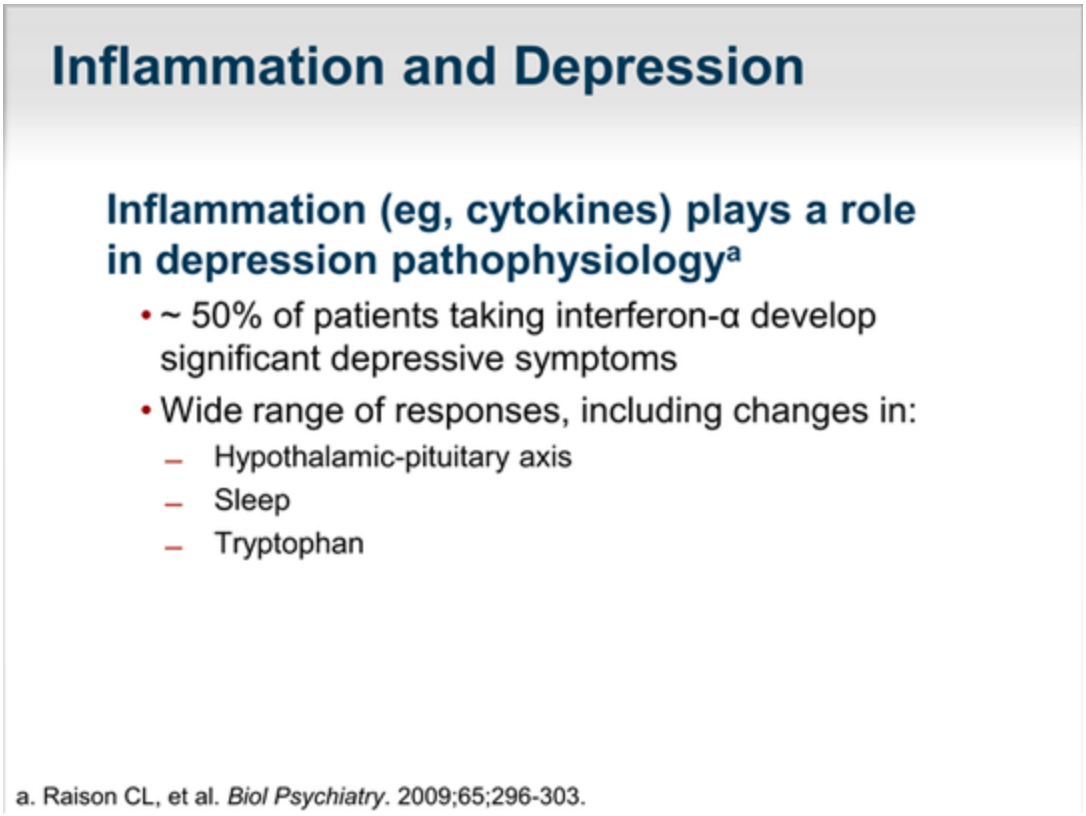
Chuck, you have been involved in some fascinating research on the potential role of inflammation in major depressive disorder. Could you tell us about some of the key findings?



Slide 13.

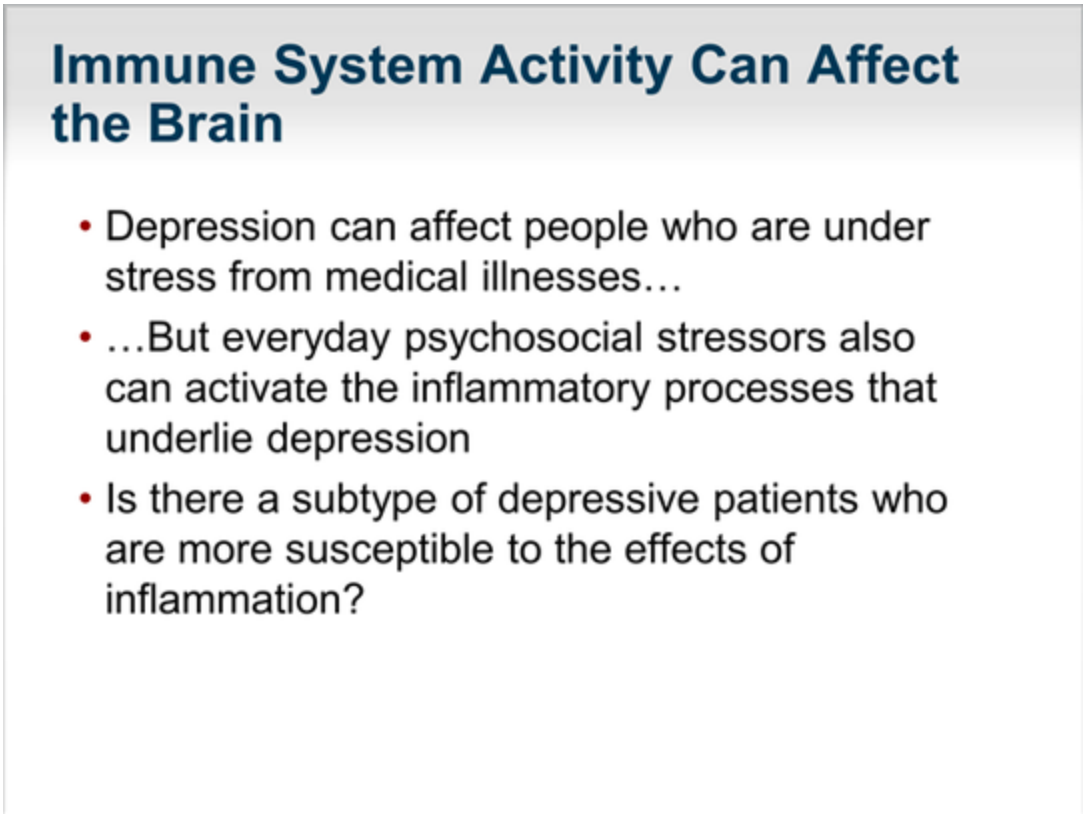
Charles Raison, MD: Increasing evidence shows that biologic processes in the body can truly affect brain function. It is not the case that everything relevant to depression occurs above the neck. It opens the possibility of accessing bodily processes as treatment modalities. That is 1 thing studying inflammation has taught us. Other things are important too. If you take large groups of people who have depression or increased depressive symptoms, they tend to have minor elevations in a wide range of inflammatory processes. You can look at various biomarkers and see a consistent pattern of increases in innate immune function that you also see as risk factors for cardiac disease, stroke, dementia, and cancer. In some ways, the physical biology of depression, at least in the periphery of the body, looks like it belongs to this family of modern illnesses that one might conceive of as

wear-and-tear disorders, where damage is being done by too much inflammatory drive and increased oxidative stress.



Slide 14.

Much evidence from a number of groups shows that cytokines tend to induce many changes in the brain and body that are stereotypic for people with depression, and these changes predict how likely someone is to get depressed with cytokine exposure. For instance, we spent a long time studying people who receive interferon-α, which is a cytokine the body makes naturally, but people take it at much higher doses for diseases like hepatitis C. Approximately 50% will develop significant depressive symptoms. But there is a wide array of responses. Some people commit suicide, while some just feel a little blue. There are strong correlations between how depressed you get with any amount of cytokine exposure and changes in the hypothalamic-pituitary axis, sleep patterns, and metabolism of tryptophan that links to serotonin. All these changes, seen in regular depression, are initiated by cytokines. Abundant evidence shows that, when activated, the immune system can affect the brain and body in ways typical for depression.



Slide 15.

When Andrew Miller and I we started this work a decade or so ago at Emory University, we thought we would identify specific types of depression seen in people who were medically sick. When you have cancer or HIV, inflammation typically occurs. But our prediction turned out to be wrong. In fact, all sorts of psychosocial stressors, even fairly minor ones, reliably activate inflammatory processes. You can measure increased inflammatory cytokine response in the blood just from participating in a session like this one we are doing now, where we are being videotaped. I can assure you that all our interleukin-6 (IL-6) levels are starting to ramp up. The more your IL-6 levels ramp up, the more likely you are to have been subjected to other things that are risk factors for depression. For instance, people who have early life adversity respond to even minor psychosocial stressors as if they have been overcome by a bacterial assault. That stress activates these same innate immune inflammatory processes suggests that the role of inflammation and depression is probably more wide-reaching than just in people who have a medical cause for inflammation.

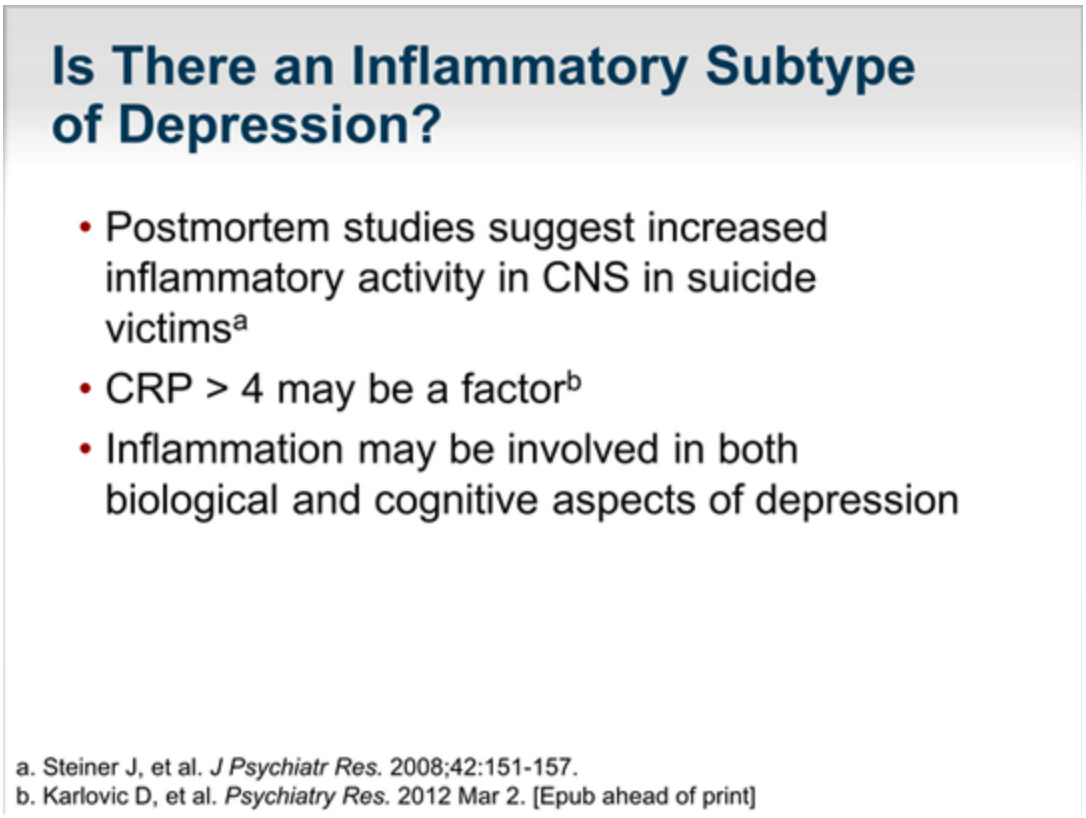
Slide 16.

The final question -- and something that we have not answered yet, although some recent data are intriguing in this regard -- is: should we think of the relationship between inflammation and depression as something that is generalized to the condition as a whole, or is it the case that we might profitably think about people with increases in inflammatory biomarkers as belonging to a subgroup of depression? I always had a bias against that, but we have just completed a study (not yet published) in which we took people who were medically healthy but had treatment-resistant depression and randomized them to receive either infusions of salt water or infliximab, which is a blocker of a very powerful cytokine called TNF-α. Infliximab does not get into the brain. All you are doing is turning down inflammation in the body. We found that on the group level infliximab worked no better than placebo for treating depression. If these results are replicated, it suggests that just throwing powerful anti-inflammatory strategies at depressed individuals is not going to be a very promising intervention. But we also found that if you measured C-reactive protein (CRP) prior to the start of the study, there was a dramatic linear relationship such that the higher the CRP, the more infliximab separated from placebo. The lower the CRP, the more placebo beat infliximab. It almost looked like a U-shaped curve.

Some evidence suggests that it may make sense to think about people who have elevations in inflammation as perhaps representing a flexible subtype that might benefit from anti-inflammatory strategies. Our study found that individuals who have elevations in peripheral markers for inflammation tend not to respond well to monoamine antidepressants. You do not need very elevated CRP. We also found they did not respond to placebo. Something about those inflammatory processes actually begins to disengage the brain from the type of social processes that you need to access placebo responses.

Dr Nelson: That is very interesting, Chuck. Some literature suggests that certain types of symptoms might be related to inflammatory processes. For example, the malaise that people feel when they have some other illness is not dissimilar to the lack of energy and dysphoria that people can experience in depression. It sounds like you view this as a more general phenomenon. But I am curious. For us clinicians, are there any symptom profiles? We're used to looking for those.

Dr Raison: What do inflammatory cytokines do? They make you sick. A small amount of evidence suggests symptom profiles, but the literature is mixed. Some studies suggest that perhaps the ties between cytokines and symptoms are a bit stronger for depression that involves neurovegetative features.



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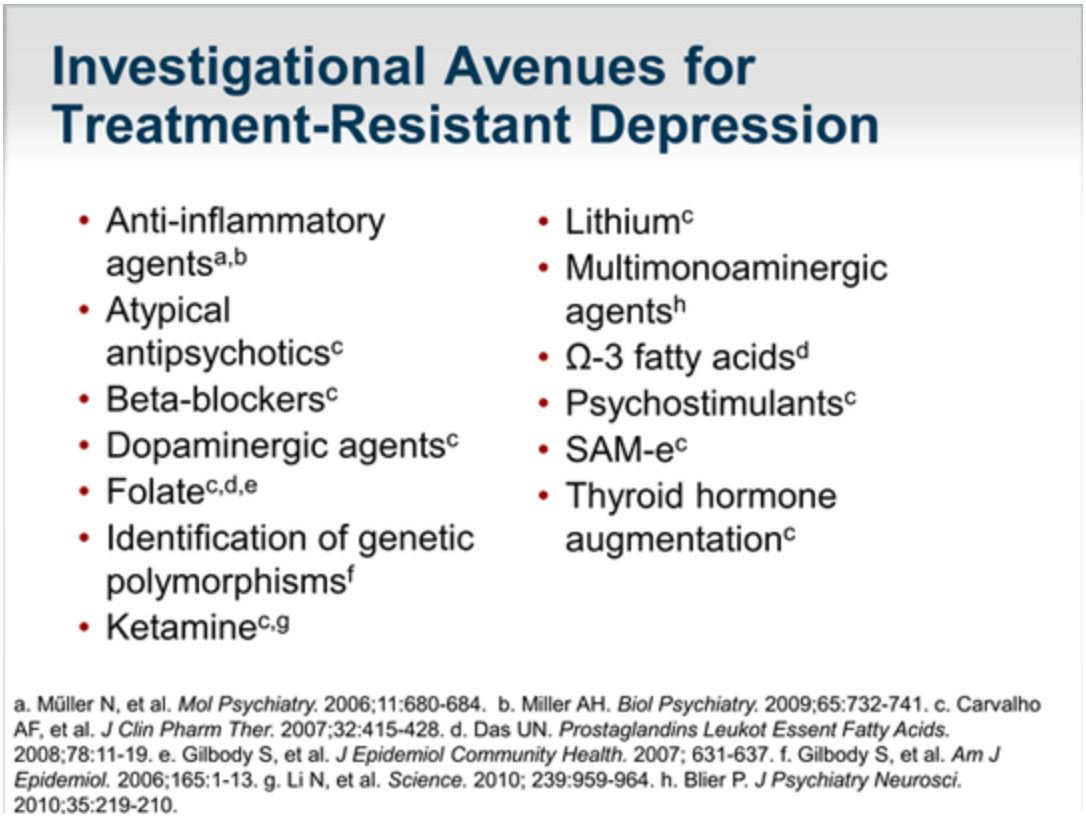
But a story is emerging about suicide and cytokines. When you look at the postmortem brains of suicide victims, you find a lot of microglial activation and increased activity of inflammatory pathways in the central nervous system. In the infliximab study, people had CRP above 4.That is where you begin to see this separation in which the anti-inflammatory strategy beats placebo. What symptoms accounted for this? Some were neurovegetative, but the signal was just as strong for depressed mood, anxiety, and suicidal ideation. Inflammation had a huge effect on suicidal ideation. At this point the data are beginning to swing back and suggest that these inflammatory pathways are probably not just involved in the "blah" feelings that go with depression but may also be intimately tied to some cognitive sets found with depression. For instance, thinking you need to kill yourself. That is as emotionally cognitive as you can get. At this point, the inflammatory story will not turn out to be especially relevant to, say, neurovegetative symptoms or symptoms that are more

common in sickness. The range will be wider.

Dr Nelson: Chuck, what are the emerging strategies for enhancing response to any depressive therapy?



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Dr Raison: There are a lot of them. We have been talking about inflammation. An emerging literature suggests that anti-inflammatory agents may offer some promise in augmenting a strategy for antidepressants. Several small randomized trials suggest that adding a COX-2 inhibitor might deepen antidepressant response.[2] However, there are other reasons to think that perhaps in some people who are depressed but who do not have higher levels of inflammation, a COX-2 inhibitor might do more harm than good. It is not clear that this will end up being universally relevant.

Other emerging biologic augmentation strategies are also linked to bodily, metabolic, and inflammatory processes. For instance, folate metabolism. In a double-blind study with a small sample [N=75] presented by Papakostas and colleagues at the 2012 APA meeting, L-methylfolate was shown to be better than placebo for treatment-resistant depression.[3] The study also looked at some genetic factors that contribute to folate metabolism and that may rather profoundly impact one's response to L-methylfolate. Folate metabolism has anti-inflammatory properties. People who do not make as much active L-methylfolate tend to have increased inflammation. In the study, people who had markers for increased inflammation and oxidative stress, or who were obese -- which is a powerful pro-inflammatory state -- were much more likely to respond to L-methylfolate than were people without those risk factors. That is an indirect way of coming around to the idea that

some pathways that we do not think about much as psychiatrists might have some gold in them, at least for patients who have suboptimal functioning in those pathways.

Augmentation strategies that address fairly specific pathways may be more amenable to identifying either genetic polymorphisms within those pathways or other factors that we know alter the functioning of the pathways. An intervention is focused on a given pathway. Some novel augmentation strategies may be more amenable to more personalized approaches to identify who may or may not respond. There are a lot of interesting possibilities. This is an area shows real promise.

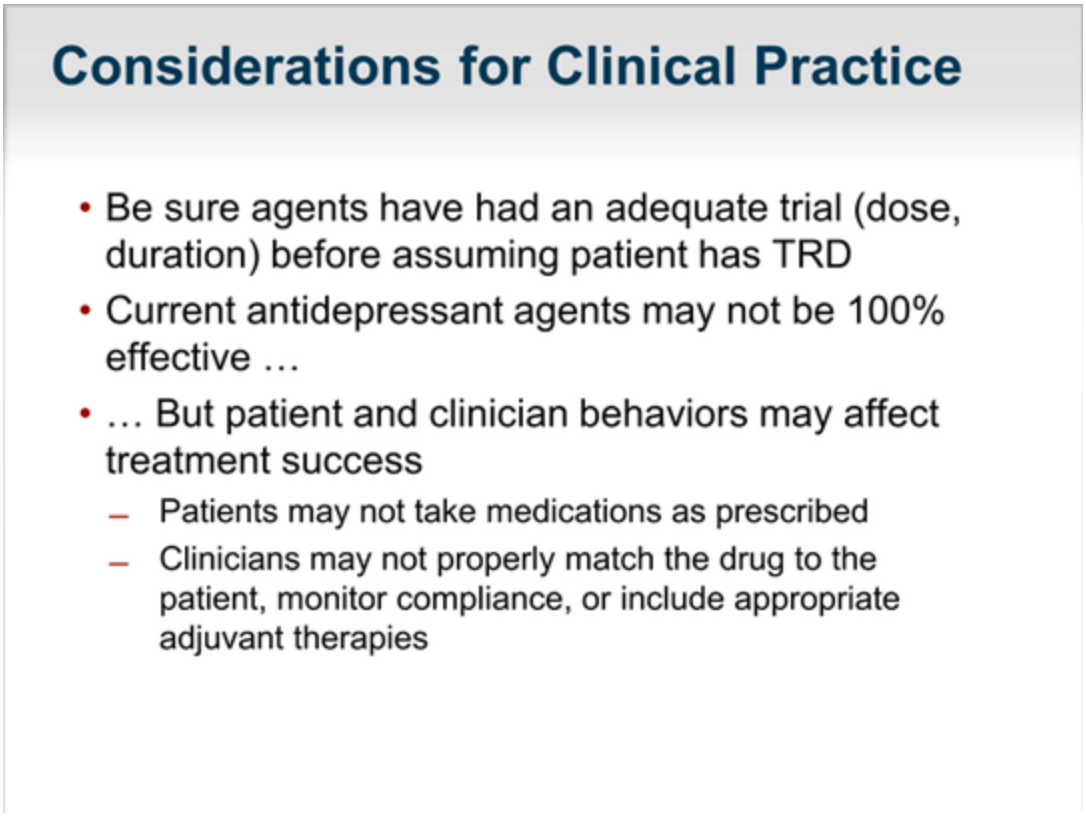
Dr Nelson: Here is our next polling question.

In your MDD patients who do not respond to first-line treatment with an SSRI or SNRI, which of these strategies would you most likely offer as a second-line approach?

- Titrate the dosage upward
- Switch to a different SSRI or SNRI
- Switch to another class of antidepressants (eg, tricyclics)
- Add adjunctive therapy with an atypical antipsychotic medication
- Use a complementary/alternative therapy (eg, exercise, nutrition)
- None of these

Submit

Dr Thase, how we might apply some of the ideas we have heard today to clinical practice?



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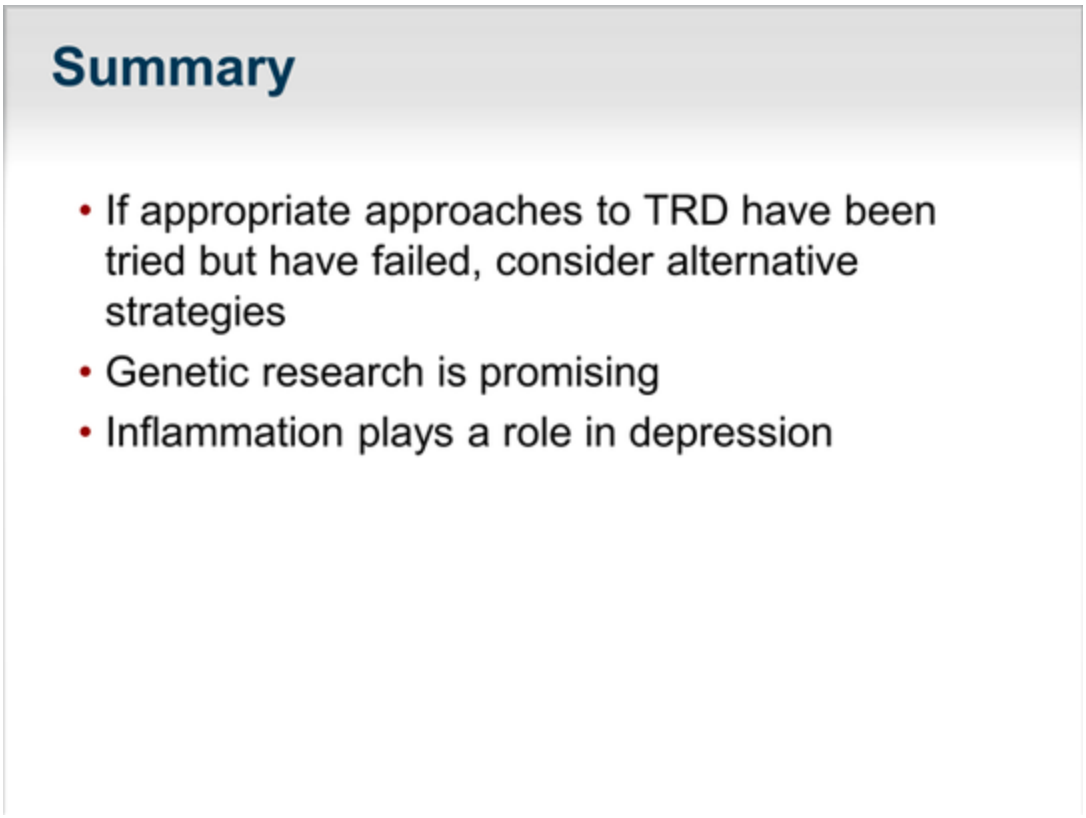
Dr Thase: Being open to novel mechanisms is the most important way. For example, I was thinking of a patient I have, who has treatment-resistant depression and evidence of a chronic infectious process whom I might be more likely to give an anti-inflammatory medication to. I want to make a cautionary statement: in our pursuit for novel therapeutics, we should not lose track of the principles of providing good care and ensuring that, before we declare someone to be treatment-resistant to first- and second-line medicine, we have made sure the patient has adhered to the medication, that we have recommended an adequate duration of treatment and an adequate dose, according to the prescribing recommendations, and that we have looked for other comorbid conditions that might be masquerading as treatment-resistant depression. In the universe of people who are said to have treatment-resistant depression there is an important large subuniverse of people who simply have not had a single adequate trial with an approved standard medication. As we look for the blue skies, we also still need to ensure that we do what we know how to do well.



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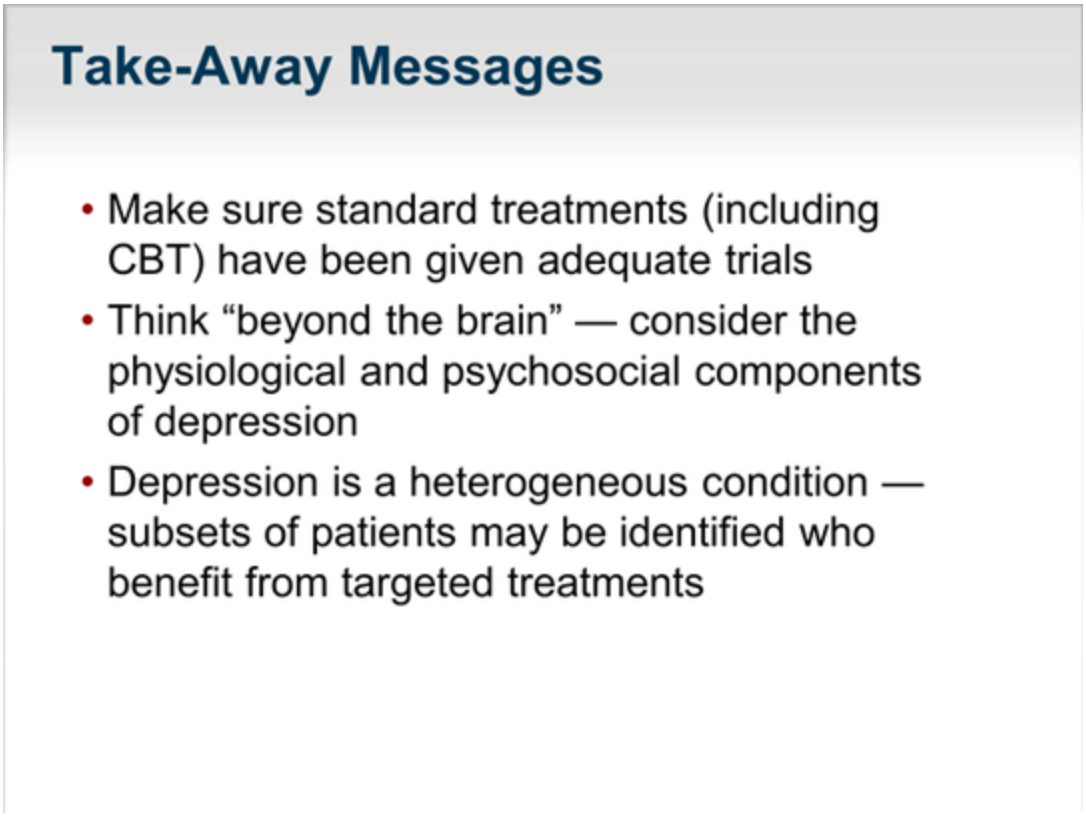
Dr Nelson: Let me summarize some points we have heard today. Dr Thase has told us about an emerging array of potentially novel treatments and the start of a move away from giving 1 monoamine reuptake inhibitor after another. At some point, he says, we need to start thinking about alternative treatments. At the same time, we need to ensure that our initial treatments have been done adequately and that patients receive the appropriate medicine and regimen. We have heard about emerging genetic findings and strategies to better understand the biology of depression but, with the exception of genes involved in the pharmacology of drugs and how they are metabolized, this is still at a research level and not ready for clinical primetime.

We have also heard about inflammation as a physiologically associated finding in depression that may explain some symptoms of depression and may lead to other forms of treatment. As we are finishing up, could each of you give the audience a suggestion, a final message to take home with them?



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Dr Perlis: I would underscore what Dr Thase has said about making sure that this really is treatment-resistant depression, that the diagnosis is correct but also that patients have adequate trials. Were they taking the medication? Have I tried nonpharmacologic strategies like cognitive behavioral therapy? I am amazed at how often people come for consultation with so-called "treatment-resistant depression" and the intervention that works is a standard antidepressant, because it was not actually tried.

Dr Raison: I agree. We must bracket our discussions on pie-in-the-sky therapies from simple things we have known for a long time. As a profession, perhaps we have been overfocused on the brain. We talk about psychiatry as being brain illness. Bodily processes may play important roles; we have not examined them as much. They may have a lot of traction that we just have not discovered yet. A take-home message is that, as a field, we should keep our eyes on a wider array of physiologic processes and probably social processes too. There may be untapped gold that, at least for some patients, we might be able to access in ways that will amp up their treatment.

Dr Thase: Depression is a heterogeneous condition. Although we have many good treatments today, we have no broadly and uniformly effective treatments. Whether you are talking about genetics, life experience, or inflammatory interactions, there may well be meaningful subsets of patients who will respond to interventions that are just beginning to be studied or have not yet been discovered. There are grounds for tempered optimism looking ahead.

Slide 22.

Dr Nelson: I would like to thank the panelists today for this very interesting discussion and the audience for participating in this activity. The audience may now take the CME/CE posttest by clicking on the "Earn CME Credit" link. Please also take a moment to complete the program evaluation that follows. Thank you.

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APA = American Psychiatric Association
CBT = cognitive-behavioral therapy
CRP = C-reactive protein
FDA = Food and Drug Administration
GENDEP = Genome-Based Therapeutic Drugs for Depression project
IL-6 = interleukin-6
HAM-D = Hamilton Rating Scale for Depression
MARS = Munich Antidepressant Response Signature project
MDD = major depressive disorder
NMDA = N-methyl-D-aspartic acid
SAM-e = s-adenosylmethionine
SNRI = serotonin-norepinephrine reuptake inhibitor
SSRI = selective serotonin reuptake inhibitor
STAR*D trial = Sequenced Treatment Alternatives to Relieve Depression trial
TNF-a = tumor necrosis factor-a
TRD = treatment-resistant depression

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3. Papakostas GI, Zajeck JM, Shelton RC, et al. Use of adjunctive L-methylfolate as personalized therapy in SSRI-resistant major depressive disorder. Program and abstracts of the American Psychiatric Association 2012 Annual Meeting, May 5-9, 2012; Philadelphia, PA. Abstract NR9-46.

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