Guest: Ronald S. Duman, Ph.D., is Professor of Psychiatry and Neurobiology, director of the Abraham Ribicoff Research Facilities, and the Jameson endowed Professor at Yale University. His work has characterized the molecular and cellular basis of stress, depression, and antidepressant treatments, leading to a neurotrophic and synaptic hypothesis of depression and a framework for the development of novel therapeutic agents. Duman has received the Anna-Monika Prize, Nola Maddox Falcone Prize, Janssen Prize, NIMH MERIT Award, and NARSAD Distinguished Investigator Award, and is a member of the National Academy of Medicine. He has authored over 300 original articles and reviews and has given over 250 invited lectures.

Host: Bill Glovin serves as editor of *Cerebrum* and the *Cerebrum Anthology: Emerging Issues in Brain Science.* He is also executive editor of the Dana Press and *Brain in the News*. Prior to joining the Dana Foundation, Mr. Glovin was senior editor of *Rutgers Magazine* and editor of *Rutgers Focus*. He has served as managing editor of *New Jersey S*uccess, editor of *New Jersey B*usiness magazine, and as a staff writer at *The Record* newspaper in Hackensack, NJ. Mr. Glovin has won 20 writing awards from the Society of Professional Journalists of New Jersey and the Council for Advancement and Support of Education. He has a B.A. in Journalism from George Washington University.

Bill Glovin: Some have called ketamine the most important discovery in half a century. Ketamine was first synthesized in 1962 and patented for use as an anesthetic in humans and animals four years later. The drug was used as a battlefield anesthetic for US forces during the Vietnam War and is commonly used by veterinarians as an animal tranquilizer. But in the past few years, ketamine has been reborn as an antidepressant. Trials consistently show that it reduces the symptoms of depression, often in the 10 percent to 20 percent range of people who have failed to respond to other drug treatments, and in emergency situations where ketamine can rapidly reduce suicidal thinking, possibly for up to three months. Ketamine has also proved to be a safe, effective and crucial way to potentially reduce fear, depression, pain and suffering in the terminally ill.

Welcome to the *Cerebrum* podcast. I'm *Cerebrum* Editor Bill Glovin, and our guest today is Ronald S. Duman, author of our recent Cerebrum article, “The Dazzling Promise of Ketamine.” You can find Ron's article at dana.org.

Ron's at Yale University, where he's professor of psychiatry and neurobiology and director of the Ribicoff Research Facilities. His research includes the molecular and cellular basis of stress, depression, and anti-depression treatments. He has authored over 300 articles and reviews, and has been invited to lecture at least 250 times.

Welcome Ron, and thanks again for all your really fine work on the article. Let's begin with depression. We see stats that say 350,000,000 people worldwide suffer from depression but only 30 percent of those people respond adequately to antidepressants. How accurate are those numbers, in your view?

Ronald Duman: Thanks for having me on, Bill. I think the numbers are very accurate. There has been a lot of epidemiology work done on depression and treatment response, and some very large studies done recently that have come up with this number of approximately 30 percent responding to the first trial of an antidepressant, a typical monoaminergic drug. With subsequent trials, that number gets up to

about two-thirds, but that can take months or even years to get the right antidepressant treatment, and to achieve a therapeutic response. Leaving about a third of patients that don't respond.

Bill Glovin: Do you agree with the claim that, even though it's about 60 years ago, that ketamine may be our most important drug discovery since that time?

Ronald Duman: It's a really interesting area to think about, because the drugs that we have now work on monoamine neurotransmitter systems in the brain. Basically, drug discovery and drug development since the 1950s has been to refine the mechanism of the target of those agents. The drugs that are on the market and highly prescribed now, such as the serotonin reuptake inhibitors, are largely derived from those original antidepressants from back in the 1950s. There really hasn't been anything new mechanistically since those early times, and while those drugs have been effective, as we had mentioned earlier they can achieve a therapeutic effect in about two thirds of patients. There's still a very large, third of depressed patients that do not achieve a therapeutic response.

The other big limitation of these drugs is they have to be administered for several weeks or months before a patient starts to feel an improvement in symptoms. That lack of overall efficacy as well as the timeline for therapeutic response are significant limitations, particularly in a population that can be prone to suicide and having suicidal thoughts.

Bill Glovin: What's the relationship between ketamine and the FDA?

Ronald Duman: Ketamine is an approved drug for, of course, anesthesia in humans, both adolescent and geriatric patients. It's also approved for treating chronic pain, so there are pain clinics that administer ketamine for chronic neurological pain. It is approved for these certain circumstances, and in fact many people are reaching out to these pain clinics to receive ketamine for their depression, to improve depression in patients that have not responded to these other typical antidepressants.

There is a nasal application of the S stereoisomer of ketamine that's being developed by Janssen that has received breakthrough status from the FDA. It looks like that is going to be effective as ketamine as most of the research trials that have been done has been administered by IV approach. So, it has limited the more widespread use, because it has to be done in a hospital or a clinical setting. This nasal application will broaden and make it much more readily available for a wider patient population. It's in the works, and there's a good chance that by early 2019, the nasal application will be approved by the FDA.

Bill Glovin: Are pharma companies working on any other derivatives?

Ronald Duman: Yeah. I think as we started out talking about why ketamine is such a significant advance, I would consider the biggest advance since the 1950s, is that it has a completely novel mechanism of action. It acts on a glutamate neurotransmitter receptor, the NMDA receptor, by blocking the channel and blocking the entry of calcium through that channel. That has led to a great deal of interest in drug development and other similar targets on that NMDA receptor channel or other allosteric sites on the NMDA receptor that might act similar to ketamine in producing a rapid antidepressant effect but with fewer side effects than ketamine.

Bill Glovin: Is ketamine as addictive as, let's say, opioids?

Ronald Duman: I think from what I understand is that ketamine is a drug that is abused. There's no question. It's referred to as Special K on the street, it is an abused drug. It doesn't really have the addictive properties of a drug like opiates, morphine, heroin, or even psychostimulants like cocaine. It definitely presents a problem in terms of its abuse potential, but it's really not addictive per se like opiates or psychostimulants.

Bill Glovin: If I'm not depressed and I get this Special K on the street, what's it going to make me feel like?

Ronald Duman: It is referred to as a dissociative anesthetic. It's sort of that mind-body separation. You feel like you're looking down on yourself, but your mind is removed from your body, the best way I can think of describing a dissociative drug like ketamine. It also produces psychotomimetic effects, it's not a hallucinogen like LSD, but it does produce psychotic-like symptoms that some people find appealing and enjoyable. Many people don't like the feeling, in fact, many patients don't like it, but they would still prefer to seek treatment and seek ketamine administration, because it's the only thing that works for them to improve their depressive symptoms.

Bill Glovin: I talked to a psychiatrist yesterday who said, and I quote, "Ketamine can be miraculously effective in a day, but the problem is it doesn't last. Okay, I'm feeling better now, I don't want to kill myself. The question is, how long will it last?" unquote. So what is the potential for longevity?

Ronald Duman: That's right. Ketamine does, it acts within a matter of hours in some people, maybe a little bit longer. On average I think it's two to four hours after a single dose, which is really an incredible finding. It's really ... I think for most of my career, the field of depression and antidepressant treatment considered a rapidacting agent like this was not possible. That in and of itself is really an incredible advance for the field. On average, people stayed better after a single dose for about a week. That can vary from individual to individual, from anywhere from three days to seven days. Some people a little bit shorter, some a little bit longer.

There is that question, and that issue, about ketamine, that you do have to go back to the clinic, using the current route of administration, the IV administration, about once a week or once every other week to receive another treatment. That is another limitation. There are some studies showing that dosing two or three times a week, people remain effectively treated. In those studies, they also found that people didn't relapse as quickly. Often, many people stayed better for almost three weeks after that two or three times a week treatment for two weeks.

The thought going forward is, for something like the nasal S ketamine, that you would probably come in as needed to receive the dosing, you could do it just in the doctor's office, so that the availability and the effectiveness or ease of taking the nasal would be much easier than taking the IV treatment. In these new compounds that people are developing, the goal is to develop a ketamine-like compound that has fewer side effects, that doesn't have the psychotomimetic, dissociative effects, wouldn't have the abuse potential that ketamine has. There are a few agents like that that are in the pipeline, they're actually phase two or phase three trials now. The hope with this is that we'll have some additional compounds that could be administered on a regular basis without any issue of side effect, or less side effects at least, and without the abuse potential.

Bill Glovin: Is your lab involved with any of these trials, or what is your research situation with ketamine now?

Ronald Duman: Our lab, we're primarily focused on studying mechanism of action. Our studies are in rodent models, where we can look at changes in the synaptic neurochemistry, the synaptic morphology, and the behavioral effect of agents to try to understand how these new drugs, these very new, very different mechanistically types of antidepressants are able to produce this very rapid antidepressant response. We are not involved in any of the clinical studies, but we're looking at several of these compounds to see how they overlap or how they're different from ketamine in terms of their synaptic effects.

Bill Glovin: I was looking at this New York Times article, but it was kind of dated. It's three years old at this point, but it was saying because ketamine has been approved for anesthesia, doctors are allowed to use it off-label to treat depression, but they charge from $300 to more than $1,000 per treatment, and insurance rarely covers the cost. Are there economic considerations regarding ketamine going forward?

Ronald Duman: Absolutely. Again, if you have the means, people who don't respond to the approved antidepressants can go out and seek treatment, as I mentioned, at maybe a pain clinic. Things are beginning to change in the landscape here in Yale New Haven Hospital. There's a clinic that's been open now for about a year where you can come in and, under a psychiatrist’s supervision, receive ketamine administration. It is now approved for coverage by the insurance companies, so that's a big step forward. It's still very expensive, I think here at Yale New Haven

Hospital, it's probably a little over $1,000 per treatment, but when you think about the ... For the insurance companies, the trade-off is that these are people that are really sick, very depressed, and could end up in the ER or in the hospital. For them, it's still worthwhile, and it makes economic sense, to cover the cost of the ketamine administration.

Bill Glovin: Anything I left out?

Ronald Duman: No, I don't think so. We covered most of the important issues.

Bill Glovin: All right. Well, I know how busy you've been, and I really appreciate you making some time for this.

Ronald Duman: Pleasure.

Bill Glovin: And thanks a lot for the article, and all your good work, and your great attitude about it. And good luck.

Ronald Duman: Thank you.

And that's our Cerebrum podcast for this month. Before we go, I just wanted to remind listeners that it's a cinch to register for a free online subscription of Cerebrum. Just go to dana.org and in the middle of the homepage, you'll see a link to our current Cerebrum article on the evolution of the human brain. Just click on the link, and the article will open with an easy to find subscription box in the right-hand margin. All you need is to put in your email, and voila, we will be sending you our email blasts and notifications when a book review or a podcast publishes.

I'd also like to say congratulations to all my Dana Alliance colleagues who yesterday celebrated the 25th anniversary of its founding. For those unfamiliar with us, the Dana Alliance for Brain Initiatives, otherwise known as DABI, is an organization comprised of neuroscientists dedicated to advancing public awareness about the progress and promise of brain research. Membership is by invitation only, and I think now there are more than 400 members.

Anyway, thanks for listening. I'm *Cerebrum* editor Bill Glovin, wishing you a great day.