Loren Roth: This podcast is for informational and educational purposes only and is not to be considered medical or behavioral advice for any particular patient. Clinicians must rely on their own informed clinical judgments when making recommendations for their patients. Patients in need of medical or behavioral advice should consult their personal healthcare provider.

Loren Roth: Good day and welcome to the UPMC Western Psychiatric Hospital Podcast series. Our subject today is geriatric depression, treatment and risk for dementia. And my guest is Dr. Jordan Karp, whom I will introduce shortly.

Loren Roth: I am Dr. Loren Roth, a distinguished professor and a senior psychiatrist at the hospital. This podcast series presents innovative research and patient centered programs at the cutting edge of psychiatry and the behavioral sciences of special interest and diverse professionals and the interested public.

Loren Roth: Our hospital and clinics are the behavioral health psychiatric division of the UPMC health system in Pittsburgh. The hospital houses the wide ranging missions, clinical, educational, and research of this UPMC specialty hospital and the nationally known Department of Psychiatry here at the University of Pittsburgh School of Medicine.

Loren Roth: As I noted, our guest today is Dr. Jordan Karp. Dr. Karp is an associate professor of psychiatry, anesthesiology, and clinical and translational science at the University of Pittsburgh and the UPMC Western Psychiatric Hospital. Jordan is the go-to person here regarding late life mood disorders and pain. He is the principal investigator of an ongoing PCORI grant on late life treatment resistant depression and its relationship to dementia.

Loren Roth: Well, congratulations and welcome, Dr. Karp. Perhaps we could begin this conversation by your explaining exactly what are the typical manifestations of late life depression, and how potentially can it be treated?

Jordan Karp: Sure. Well, thank you for having me here today, Loren. It's a pleasure to be a guest on your podcast. I think that there's some similarities between late life depression and depression that presents in younger adulthood, but there's also some unique features. So let's talk first about some of the similarities.

Jordan Karp: I would say that many older adults present with depression that's similar to their younger counterparts. So a sustained period of depressed or low mood and a decreased pleasure in previously pleasurable activities, this is frequently presents with problems with sleep, in particular insomnia or hypersomnia and increase in fatigue during the day, loss of appetite and weight loss, poor self esteem, and perhaps the most problematic symptoms of depression include thoughts of death or dying or active plans to kill themself or to have committed suicide. Some unique features of late life depression are apathy. So a difficulty with motivation. Worsened disability that's probably out of proportion to the

extent or severity of the depression and psychomotor slowing, which can manifest as slowed reaction time and also, quite obviously, as slowed gate.

Loren Roth: I see. Well, you've given really a full and excellent account here of what it is to be depressed, and especially if one is older. By the way, where would you say or place the idea of an older person? Is that age related or something else?

Jordan Karp: Well, I think that clinically we often think of older adults as maybe a little arbitrary but 65 or older. This is when Medicare kicks in. This is often when people retire so there's a shift in life circumstances, and this is also when co-morbid medical conditions often become worse, such as arthritis, diabetes, high blood pressure, cancer, chronic pain, which can also worsen the experience of depression and contribute to a mutually exacerbating nature between these medical conditions and mood and anxiety problems like depression or generalized anxiety disorder and co-morbid cognitive decline. It also depends on whether people have been depressed or medically ill throughout their life.

Loren Roth: Would you just make the comment perhaps briefly about old-old? I've heard that, and that's what geriatricians say. Does that have relationship to the subjects you presented so far with respect to depression?

Jordan Karp: I think so. So old-old are often defined as people 85 years of age and older. I think that some of the characteristics of people that are 85 and older are that they often have more medical problems. Age is the number one risk factor for cognitive decline and dementia. So the prevalence of cognitive disorders and dementing illnesses is higher in this age group, and these people are often more frail. I would say that there may be a differential response to antidepressants and some antidepressant treatments for people in the old-old age group.

Loren Roth: Well, that also is interesting to me because when I began to be a psychiatrist, old-old was defined as 75 years old. So that really is another manifestation of some improvement, let's put it that way, from a population base at least of our ability to function most effectively.

Jordan Karp: People are living longer, healthier.

Loren Roth: Great. Now I know you also are an expert in the area of late life treatment and approach with respect to resistant depression, and perhaps you'd like to expand a bit on that area about resistant depression in the old and the old-old and what it means to you and how you think about such patients and what interventions we might do?

Jordan Karp: Sure. Maybe it makes sense to first-

Loren Roth: One at a time. I shouldn't have given you three different-

Jordan Karp: That's all right. We can start with defining treatment resistant depression.

Loren Roth: Great.

Jordan Karp: So the way my geriatric psychiatry colleagues and I define treatment resistant depression is failure to have meaningful clinical response to at least two antidepressant medications prescribed at an adequate dose and duration. And that seems to be the norm rather than the exception for the majority of older adults because 50-80% of older adults do not respond to first or even second line treatment with an antidepressant. That doesn't mean we can't get these people well. It just means that there's probably an interaction with brain changes and medical problems and psycho-social circumstances that may make depression a little more challenging to treat in older adults.

Loren Roth: Well that is very significant comment, and also kind of a brief summary of where we are in the field. With respect to those people who have failed two antidepressants and are treatment resistant in that sense or late life, would you potentially comment on actually, "Well, this is my grandfather," or what have you, and you've explained that as a physician. And I have a grandfather say, "Well, doctor, we're still here to see you. I'm really concerned. Do you have any other suggestions how to approach my grandfather?"

Jordan Karp: Sure. So I think that the first step is to follow the oath we've all taken as physicians to first do no harm. So first is to do a thorough medication review to make sure that there's nothing iatrogenic that maybe contributing to this difficult to treat depression. So other medications such as some blood pressure medications or opioids or benzodiazepines can worsen cognitive problems and depression. So minimizing exposure to these makes sense. The second thing is to make sure that the person is actually taking what they're prescribed. Because we know that so many people get a prescription for an antidepressant and they don't actually get it filled or they don't take it as prescribed.

Loren Roth: Surely.

Jordan Karp: So making sure that they are adherent is important to assure we try to get these people well.

Loren Roth: Right.

Jordan Karp: The next step is to figure out well have they had a partial response or no response at all to what's been prescribed. And the big question here is well do we augment what they're taking or do we switch to something else. So we recommend following a stepped care approach to augmentation versus switched strategies, and if after several of these people don't get well, then we often will combine this with referrals for counseling or psychotherapy, recommendation for boosting exercise or physical activity, or social engagements, especially because so many older adults are lonely and isolated, making sure that other medical problems are optimally treated that maybe worsening the depression, in particular chronic pain or diabetes, and getting

family members engaged in treatment. Because we know when family members are engaged, patients are more likely to be adherent and less likely to drop out of treatment.

Loren Roth: Well, I can really relate to that. I can even relate to that in my mother, frankly, struggling with this type of problem. Perhaps one way to summarize what you said here is that a good geriatric physicians, really all physicians should be environmentally sensitive. Mainly they should be considering the patient in their place and what is happening to them in the sense of the social interactions. So that's one more way to go.

Loren Roth: Now, Dr. Karp, I know also you are quite expert in the issue of cognition and the problems of cognition that can be associated and frequently are with depression or for that matter dementia. But perhaps you could lead us into this field a little bit to understand better about cognitive changes and impairment.

Jordan Karp: Sure. Well, Loren, we know that being depressed at any time in one's life doubles the risk of becoming demented in late life, which really supports the need to screen for and treat depression across the age span as optimally as we can to reduce this modifiable risk factor for cognitive decline in old age. So it seems that depression in mid-life and even more so in late life is a risk for cognitive decline and dementia. But depression may also be a prodrome of dementing illnesses, both vascular disease as well as Alzheimer's. And probably 20-40% of people who develop dementia go on to also have significant depressive symptoms. So I think of depression as both a risk factor and a prodrome in late life for dementia.

Loren Roth: Yes, I follow that. So we could be seeing some of the first manifestations in certain ways when you're discussing the idea of the prodrome.

Jordan Karp: I think that behavioral and emotional and personality changes are often overlooked and not appropriately attributed to neurodegenerative and vascular changes in the brain and as a harbinger of cognitive decline.

Loren Roth: Well, I do get that idea. I've heard this term that depression is toxic to the brain, and I think in your summary there, you've run through the different ranges, for example, of how to think about that problem. Do you have anything further to add that you'd like in a kind of causal way between depression and dementia?

Jordan Karp: Well, I think that there's a couple of reasonably established theories about how depression contributes to cognitive decline and dementia. It's thought that depression does so by diminishing cognitive reserve. So we have I think a way to understand this is we have a redundant synapses and connections in our brain. Depression contributes to cognitive decline in two ways. First, depression is a high stress state, and that we know high stress is related to elevated levels of glucocorticoids, and these high levels of glucocorticoids negatively affect the

hippocampus. And the hippocampus is an area of the brain that's important for memory, and it's exquisitely sensitive to higher levels of these stress hormones.

Jordan Karp: We also know that depression is an inflammatory state, which contributes to vascular changes, not just in the heart and the body but also in the brain. And that contributes to some difficulties with executive functions. So we have both a hit to the memory part of the brain as well as to the part of the brain that's important for higher level cognitive function.

Loren Roth: You know as you talk about this, I realize I could listen to you indefinitely, which is really not the total way of proceeding in a podcast. So I would like just to change the topic a little bit towards this editorial that I did read that you wrote with Dr. Lenze as previously was here in Pittsburgh. We know him very well. But could you give us a little brief summary of the new type research that you're now doing that is sponsored both by PCORI and by the NIH, National Institute of Health? So that would be helpful to us. It sounds like a very bold venture to me as I've read.

Jordan Karp: So the PCORI project, and PCORI stands for Patient Centered Outcome Research Institute, has funded a five site project, and it's led by Dr. Eric Lenze at Washington University. We have sites at UCLA, University of Toronto, Colombia, and Pittsburgh in addition to Washington University. And we're trying to answer the question, what should PCPs and psychiatrists do when their patients don't respond to first or second line antidepressant pharmacotherapy? And as I said, this is the norm and not the exception.

Jordan Karp: So we're testing whether we should be augmenting or switching pharmacotherapy for these difficult to treat older adults. In this project, we're defining late life as people 60 and older, and we're comparing people who are younger old, so 60 to 75, and older old, in this project we're defining old-old as 75 and older to see if there's a differential response. And then we'll also be able to do subgroup analysis to determine who is more likely to have a change in their cognitive decline over the course of two and possibly even longer years of follow up.

Loren Roth: So this is a large study, and it's very well funded, correct?

Jordan Karp: Yes. It will be the largest study of treatment resistant depression in late life ever. We're recruiting 1500 people in North America.

Loren Roth: Wow. I also noted that you did have kind of two different monikers or ways of describing your research. One was the Optimum Study, and the other was the Optimum Neuro Study. You want to just distinguish between the two of those briefly for us?

Jordan Karp: Sure. The Optimum Study is the project that's a clinical trial, that's an effectiveness study, that's funded by PCORI, and our main outcomes are

improvement in depression, improvement in patient reported well being. We also have a focus on safety and falls because when we develop the study, that's what patients told us were important outcomes to them. The Optimum Neuro Study is funded by the National Institute of Health, and that's where we're following cognitive trajectories over the course of at least two years with neuro psych as well as imaging and inflammatory markers to see if we can determine the profiles of these patients over time.

Loren Roth: Well, we're just about going to close. So I would just like to ask you one final question. Given your devotion to geriatrics depression and the career and all that you've mentioned so far, including dementia, could you just give us a few words about how you chose this career? What happened that rendered you so interested or expert?

Jordan Karp: So I've been blessed that I kind of knew that I was interested in geriatrics from the time that I went into medical school because of the strong mentorship that I had working with geriatric psychiatrists here at the University of Pittsburgh, in particular Chip Reynolds who really influenced my thinking about the specialty care of these patients. I've been drawn to this area of medicine because it really takes a big picture approach to thinking about these problems. So it's thinking about psychiatry, medicine, neurology, functioning, family systems, and how people live and interact with their environment, and that's very appealing to me.

Loren Roth: Well, in closing, I kind of would say, well you offer the skills of what I like to call a complete physician who has all of that behavioral science and all of that psychotherapeutic input and all that medical knowledge broadly speaking. And really that is what it takes to take care of an older patient.

Loren Roth: Well, we very much appreciate you being with us today, Jordan, and for our listeners, I will note that this podcast as well as some of the background scientific information in journals and what have you will all be placed on the UPMC website, specifically the UPMC Western Psychiatric Hospital part of that website, as well as the departmental website of the Department of Psychiatry at the University of Pittsburgh. And we thank you very much for being with us today.

Jordan Karp: Thank you for having me.