[MUSIC PLAYING]

JORDAN KARP: So I'm going to speak about systematic approaches to improve outcomes for pharmacotherapy in late-life depression. This is something that I think about, really, on a daily basis. This is how I earn my bread and butter.

So we need to remember that late-life depression is one of the few medical conditions in which treatment can make a rapid and really dramatic difference in an older person's quality of life and level of functioning. And we can never give in to therapeutic nihilism because even though 50%, and maybe up to 80%, of older adults don't respond to first- or second-line antidepressant pharmacotherapy, we can get people better.

So this is what I'm going to talk about today. I'd like to argue for a systematic approach to getting these people well. So we often call this a protocol, or an algorithm, or a clinical pathway, or using a stepped care versus an individualized approach. And we often call this usual care.

And then we'll move on to talking about defining one's own private formulary and protocol for late-life depression. So we'll talk about first- and second-line interventions, how long each step should last, and switching versus augmentation. And I'd like to do a deep dive into a project that we conducted here at the University of Pittsburgh called the IRL-GRey study, which stands for Incomplete Response in Late-Life Depression-- Getting to Remission.

And then people want to know what's new and what's the new research that's going on. So we'll wrap up with a discussion of our ongoing study called OPTIMUM, which is a study for treatment-resistant depression in older adults and the next step that primary care physicians should take.

So I like this statement by Tom Insel, who is the past NIMH director. And this was the last post on his blog in 2015. And he wrote, "How do we improve the quality of mental health care? We can do much better by delivering the treatments that we have today. We can save lives, many lives, simply by closing the unconscionable gap between what we know and what we do."

And that's what I'm hoping I'll convince you today, that we have lots of evidence for what works that's been learned in the laboratory and the research clinic that has not been implemented and disseminated into primary care and real-world settings.

So let's start with a tale of two approaches. And we'll start with what we usually do. And what we usually do is deliver usual care. And I am guilty of this too. This is what I do if I'm in a busy clinic, quite frequently.

So much of our approach may be based on the "fad du jour." So it might be based, our approaches may be based, on what we've just read in a journal or what a drug rep has just told us about a fabulous new medicine that's come out, but we don't have all the safety data about it yet.

It's also based on little cumulative experience due to small numbers of patients receiving many different medications. It's often informed by ill-advised or ill-timed changes in treatment that may reflect pressures from the patient or their family to switch medicines more quickly.

And finally, the focus is on the treatment, often as a result of clinician bias. And the focus is not on the patient as often as it should be because making decisions based on measurement-guided care can be exhausting. So what we do know is that a systematic approach is superior. And that's what I'm hoping to convince you of today.

So this is based on best evidence or guidelines. It's also based on clinical experience that's based on a large number of patients from FDA registration trials and phase IV clinical trials. The goal is to keep the course. And this protects the clinician from their own personal biases and from pressures of patients and their families. And again, the focus is on the patient.

So as we get started with this discussion, we need to talk about whether treatments for depression actually work. And I like this systematic review of the efficacy of treatments as well as different kinds of controls for depression. And this was a large review that included over 10,000 patients receiving acute treatment for their depression.

And if we look at the y-axis, this is the percent symptom reduction in their depression severity scores. And let's just focus on the blue bars because these reflect studies that had blinded raters. So the raters weren't biased because they didn't know what kind of treatments the patients were getting.

So if we look at the left side of the figure here, this is combination treatment-- so a combination of medications, antidepressants, along with psychotherapy. And this is the best. It seems that there is a reduction in depression symptom severity of over 50%.

This is better than antidepressants alone and psychotherapy alone. However, antidepressants and psychotherapy alone in these clinical trials-- so these are trials where patients were coming in weekly-- really were not better than alternative therapies. And the alternative therapies included controls such as exercise or acupuncture.

And they really weren't that much better than intervention controls either, which included things like bibliotherapy, or bringing people in for healthy counseling about approaches to aging, or sham acupuncture. They were better than treatment as usual, just having people follow up with their primary care doctor.

And they were better than waiting lists-- so just saying, I'll check up on you in 12 weeks. If patients received a pill placebo, they often got pretty much better as well. So there's some common elements to both the active treatments, the antidepressants, the empirically guided psychotherapies, and these other kinds of control conditions.

So patients come into the clinic. They're given a thorough evaluation. They're given an explanation for their problem. They're given an expectation for hope. And then they come in regularly on, usually, a weekly basis with this ritual with an expert healer that goes on. And it's an active engagement in the process.

I think we could be both frustrated by these results and say, oh, this is a real bummer that our active treatments don't seem to be that much better in reducing depression symptom severity and then these controls. But we could flip the coin and look for some common elements that are common across all of these parts of these clinical trials and say, well, actually it's pretty good that if we can get patients engaged in an active treatment program, we can reduce depression symptom severity by 40% to 50%.

Well, let's move on to talk about psychotherapy for late-life depression. Now, it's commonly accepted that most psychotherapies are empirically based. Manualized psychotherapy, such as problem-solving therapy, interpersonal psychotherapy, and cognitive behavioral therapy, work for late-life depression. But it's difficult to make this conclusion without looking at the controls that were used as comparisons against these active interventions.

So the authors of this study looked at the within-group changes for these active interventions. And if we look at the left side, this is the wait list kind of control where they say, see you later. I'll talk to you in 12 weeks. Next to that is treatment as usual, follow up with your primary care doctor, and I'll catch up with you in about 12 weeks.

These patients didn't really get that much better. But when they compared patients to attention control where they brought patients in on a regular basis and provided an intervention that was not maybe depression specific but it was engaging, if they were involved in a pill placebo control because there was also a medication arm, these patients had improvement.

And patients really improved if they were exposed to supportive psychotherapy. So supportive psychotherapy may be the best kind of control condition for comparing against active psychotherapies like CBT, or PST, or interpersonal psychotherapy. And it may be because of the attention, the education, the reassurance, the monitoring of symptoms, the provision of motivational interviewing, and the praise to support self-esteem and healthy behaviors that is part and parcel of supportive psychotherapy.

So what they observed is that the standardized mean difference or their measure of the effect size is that there was really a range from 0.1 for the wait-list control-- patients didn't get better-- up to 1.1 for those receiving supportive therapy. Really, these patients who received this kind of control got a lot better.

Psychotherapy compared to all of these controls really was a potent intervention with an effect size of about 0.73 So patients get better if they receive psychotherapy and they're depressed. But when psychotherapy was compared to the supportive psychotherapy, it really watered down the effect size. So still meaningful, but it really suggests that much of these nonspecific ingredients that are provided are really an important part of the intervention.

So the way I interpret this is that putting people on a wait list or treatment as usual did not help depressed patients. And this is really consistent with the previous study I just showed you about medications and psychotherapy. Empirically based psychotherapy works for late-life depression, and it's superior to a variety of controls, even potent supportive psychotherapy. But active controls or active interventions in which patients are actively engaged in a therapeutic program really seems to have benefit.

So let's move on to talking about some systematic approaches. So we call this, again, clinical protocol versus an individualized approach or usual care. And I'm going to talk about two different projects. So one is the IMPACT project that I'm sure many of you have heard about and read about, which stands for Improving Mood-- Promoting Access to Collaborative Treatment. And the other is the PROSPECT study, which stands for the Prevention of Suicide in Primary Care in the Elderly-- a Collaborative Trial.

So we're going to start with the IMPACT study. And this was a large study of 18 primary care clinics, mostly on the West Coast of the United States. And they randomized 1,800 people with different kinds of depression, either major depression, dysthymic disorder. And the majority of them had a combination of the two, both major depression and dysthymic disorder, which is sort of a chronic, low-grade, smoldering depression.

Half the patients were exposed to receive the IMPACT interventions. So the IMPACT intervention was exposure to 12 months with a depression care manager. And this depression care manager was supervised by a psychiatrist and a primary care expert.

And then they provided recommendations to the primary care physician about what medication should be prescribed, usually an SSRI. And if the patient, and according to the predetermined algorithm, suggested this, then they could also provide problem-solving therapy, either by phone or in person.

And the other half of the patients received usual care. The doctors were told, your patient is depressed. Do your best to get them well.

Let's look at the left side of this table. This is what the predefined or predetermined algorithm is that they followed. So there were three steps. Step one is to provide an antidepressant, usually an SSRI, or problem-solving therapy based on what the patient preferred. This was for 8 to 12 weeks.

Nonresponders then could either switch the antidepressant or problem-solving therapy. And they had an algorithm criteria for partial responders, which was to combine the interventions. After another 8 to 12 weeks, the next step was to combine the antidepressant and problem-solving therapy or to consider electroconvulsive therapy or other specialty mental health services.

And if we look at the outcomes, the rates of response, and they find responses of 50% reduction in the depression score. What they observed is after 12 months, the intervention group, those who received the depression care management, had a 45% response rate compared to those who received usual care, who only had a 19% response rate. And I want you to remember this number of a 19% response rate for usual care.

The intervention group also had more depression treatment. So they got more antidepressants prescribed. They got more exposure to problem-solving therapy than the usual-care group. They had more satisfaction with their treatment. They had better functioning and less pain. And they, overall, described a better quality of life. So the take-home point is that depression care management in the IMPACT intervention really worked.

So let's move on and talk about PROSPECT because this is, in a way, a replication of the IMPACT study. And I want to focus a bit more on PROSPECT because I think that its history of how it came to be about is interesting and also because Pittsburgh was one of the sites.

So many of you may recognize this fellow. This is Harry Reid. Harry Reid was the senate majority leader from 2007 to 2015. And Harry Reid is from Nevada, and his father was a miner. And when Harry Reid was in his 30s, his father killed himself with a gunshot wound to the head. So Harry Reid was very interested in suicide and suicide prevention. And he encouraged NIMH to pursue and promote suicide prevention research. So that led to the PROSPECT group being funded as one of the selected projects to pursue this line of work.

So the goal of the PROSPECT intervention was to determine the effect of a primary care intervention on suicidal ideation and depression in primary care patients. And they recruited 600 people from 20 primary care practices. And the locations of this study was Pittsburgh, Philadelphia, and the Westchester suburbs outside of New York City.

And very similar to the IMPACT project, patients either had major depression, minor depression, and they also had to have at least moderately severe depression defined as a Hamilton Depression Rating Scale score of at least 10.

So half the people received the PROSPECT intervention. And it was similar to IMPACT. So, but they received 18 months of exposure or access to a depression care manager who was supervised by a geriatric psychiatrist. And they would-- recommended citalopram as the first-line treatment.

And then they had an algorithm for what they should do if there was non-response or partial response. And if patients wanted, and it was part of the algorithm, they could offer interpersonal psychotherapy either by telephone or in person. And the other half of the patients received usual care.

So I'm going to show you the algorithm on the next slide. But let's just look at the outcomes. So the rate of response-- and they defined response as a Hamilton Depression Rating Scale score at less than or equal to 10. After four months, the intervention group had a 33% response rate compared to the usual care group, only 16%. So pretty similar to the 12-month response rate for the IMPACT group of 19%. So remember these numbers, 19% and 16%.

But after 12 months, those who received the PROSPECT intervention continued to respond. And those who received it had a 54% response rate at 12 months compared to those receiving usual care, who also got better, but still not as much of a response as those receiving PROSPECT.

So I'm not going to go into the PROSPECT algorithm too deeply because I'm going to share an updated algorithm with you a little later in my talk. But this is just to remind you that the investigators had an explicit plan for what they were going to do for partial or nonresponders. And this was to protect them against their own clinician bias and enter individual or intersite variabilities.

They weren't testing the different medications. They were just testing this process of care. And they wanted to protect themselves from patients or family pressures to make ill-advised or ill-formed choices.

So the PROSPECT group then continued to look not just at response rates, but they wanted to look at remission. And remission is really the goal of depression treatment because it's nearly an asymptomatic state. And this is important because patients with residual symptoms are at an elevated risk of relapse. They can still have functional impairment. And they have an impaired quality of life.

And so in this project, looking at remission, the investigators were just looking at the more severe patients-- so only those patients who came into the study who met criteria for major depressive disorder and had a Hamilton Depression Rating Scale score of at least 18. So they were a sicker group of patients. And they all had data at the four-month time point.

And they wanted to know, does the PROSPECT intervention improve rate of remission? And what were some moderators of remission? Because, remember, they were interested in the effect of the PROSPECT intervention on reducing suicidal ideation and behavior.

So what they observed is that for folks who had data out to four months that at eight months, 43% of those who received the PROSPECT intervention had remitted. They were nearly asymptomatic compared to 28% of those who received usual care-- so a statistically and clinically meaningful difference in remission rates between these groups.

What they also observed is that more hopeless patients-- and hopelessness, which you can measure, is a proxy or a marker for increased risk for suicidal ideation and behavior. So more hopeless patients were less likely to remit if they were treated in practices receiving usual care. Less anxious patients were more likely to remit only if they received the PROSPECT intervention.

So if they were more anxious, it didn't matter if they got depression care management or usual care, which suggests that maybe these kinds of patients should be referred for specialty mental health care treatment. For all patients, limitations in physical and emotional functioning predicted worse remission rates.

So the last data point that I want to share with you from the PROSPECT study is this. Because we know that a patient is not going to get well if they don't take their medicine, so the PROSPECT investigators looked at the percentage of depressed, older primary care patients who received treatment for their depression-- so either an antidepressant prescription or a receipt of interpersonal psychotherapy as a function of whether they received the PROSPECT intervention or usual care.

The red lines indicate those receiving PROSPECT. The blue lines show those receiving usual care. And what they observed is that across the entire study from four months out to 24 months, the rates of receiving antidepressant treatment was about 85% to 89% for those receiving the PROSPECT intervention and only about 49% to 59% for those receiving usual care.

Importantly, since suicide was one of the main outcomes, the PROSPECT patients had over a two-times greater decline in suicidality compared to those receiving usual care over the course of the study. And for the PROSPECT patients, treatment response occurred earlier, and it continued to increase out to the end of the study out to 24 months.

So the way I interpret this study is that sustained, collaborative algorithmic care maintains high utilization of antidepressant treatment. It reduces suicidal ideation and improves the outcome of depression out to two years. Now, I'm not showing you slides about this.

But subsequent prospect analysis, and this is 10-year-later data, shows that there's a different rate in morbidity between the two groups with those who received the PROSPECT intervention less likely to die than those receiving usual care. And one of the main differences, and there seems to be a difference in rates of cancer between the two groups. So depression treatment and collaborative care treatment seems to save lives.

So one final slide that I want to share with you about the importance of measurement-based care just because I think that this study is so cool that I wanted to talk about it today. So, and I think that measurement-based care is really a critical part of an algorithmic approach to getting depressed patients well.

So this was a study that was published in the*American Journal of Psychiatry* a couple of years ago. It's from a teaching hospital in China. And it was adult out-patients with moderate to severe depression, just 120 people. And all of the patients were only allowed to receive two different kinds of medications, either paroxetine, dosed up to 40 milligrams a day, or mirtazapine, dosed up to 45 milligrams a day. So that's all that they could receive.

However, half the patients were randomized to receive usual care. The doctors could prescribe this medicine however they liked. And the other half of the group was randomized to receive measurement-based care. So the doctors would measure the patient's depression severity and tolerability of the antidepressant, measuring any side effects, and adjust the dose up or down, and see the patient more frequently according to how they did by these measurements.

And the goal was to see if they could control the wide variations in clinicians' behavior to minimize practice bias and result in individualized and better outcomes. And what they observed, and here's-- this is the estimated mean time to remission. The yellow line shows the standard treatment, the usual care group. The green line shows the measurement-based care group.

The measurement-based care group got well. They remitted in half the amount of time. In about eight weeks, they met criteria for remission compared to about 14 and 1/2 weeks for those who received usual care. The proportion of remitters was about 74% of those who received measurement-based care and only about 29% of those who received usual care.

And to put this into perspective or a number, another way of interpreting this is the number to treat. So they only needed to expose three patients to measurement-based care to have one of them remit. Now, to just think about Dr. Applegate's talk where he discussed management of blood pressure to prevent death or a negative event, and his number needed to treat that he was presenting was between 60 and 90. So relative to that, this is a very potent and, I would say, safe approach to getting people well because there's really limited side effects to following a measurement-based care approach.

So, often when I'm talking with different audiences about this, I'll do a deep dive into going through each of these processes of care, comparing experimental conditions versus usual care. The majority of you, I think, work in primary care settings. You're taking care of a lot of other problems that these patients have.

And I know that you all care about depression, and you want to do your best. But, oftentimes, it moves farther down the problem list. And there's only limited amount of time that you have to spend with these patients. So I think that just focusing on four of these processes of care may help to improve outcomes for your patients.

So, one, selection of an antidepressant, I would restrict my own personal formulary to a small number of antidepressants based on the best evidence and used in a large number of patients. Dose titration and change in therapy, I would make this predetermined. And we're going to talk about this a little bit more. But based on operationalized criteria, then that protects you from your own personal bias, and it protects you from pressures from patients and family to switch or augment too early.

Monitoring of symptoms and side effects, again, systematic monitoring with the use of structured interviews and validated scales. And finally, I think that the main focus of clinical interaction should be to maintain treatment adherence using psychoeducation, characterizing and sharing the measurement-based care approach and the results with the patient, and management of adverse effects, and not negotiating with the patient and their family whether and how antidepressant should be used, titrated up or down, switched or augmented, and selecting different agents, keeping it simple.

So moving on, I think this leaves us two questions to consider about systematic approaches to the treatment of mental disorders. And the first question is, what's our best hope to improve treatment outcomes until advances in neuroscience yield more effective treatments or identify biomarkers that will allow us to match patients and specific treatments, for example, pharmacogenetic testing, which I'm sure many of you are thinking about and wondering

About. I don't think that the data is there to suggest that we should be using it regularly. Certainly, there's no evidence to suggest that functional MRI, really, although we use it all the time in research studies, has really any clinical utility yet.

But the next question then is, is it diligent care management with structured procedures-- and I hope that's what I'm convincing you of today-- or the specific treatment strategies that account for the differences in outcomes? And I'll continue to do research on these different specific treatment strategies. But I do think that it's the diligent care management that really contributes to superior outcomes.

So moving on, let's talk about people's own private formulary, first- and second-line interventions, how long each step should last, and switching versus augmentation. And again, I'd like to do a bit of a deep dive into the IRL-GRey project, which was conducted here at the University of Pittsburgh, which stands for Incomplete Response in Late-Life Depression-- Getting to Remission, which we published in *The Lancet* a couple of years ago.

So there are guidelines for the treatment of depression in older adults. And as Dr. Applegate mentioned, guidelines are not a moral imperative. They are a set of recommendations with alternatives.

So there's guidelines from the US. But these were published in 2001. And then there were guidelines from Canada, which came out in 2006. And I think they're excellent, and they're practical. They're getting a little stale. And we need new guidelines.

But in general, the advice is to start with citalopram or escitalopram. If that doesn't work, switch to venlafaxine, maybe add on mirtazapine or Wellbutrin. Don't forget to use problem-solving therapy and involve the family. If that doesn't work, consider electroconvulsive therapy.

So this all makes sense. Much of it is evidence based as much as it can be. But I would say a little bit more of these guidelines as evidence informed. Because if we look at response rates for different randomized placebo-controlled trials of late-life depression, really the only medications which separated from placebo are here on the left-- so fluoxetine, sertraline, paroxetine, which I never use with older adults, and duloxetine.

And what's really absent from this is Wellbutrin or bupropion or mirtazapine, which we frequently recommend as switch or augmentation agents. And we know that they work. We've extrapolated this from younger adults. But the data in older adults is missing.

What I think is interesting here is that the response rate for these drugs in these randomized controlled trials is about 40% to 45%. The response rate for placebo, the white bars here, is about 30% to 40%. So again, patients are participating in clinical trials. They come in for a full evaluation. They have an explanation for what's going on with them. They're given hope for the future. They have this healing ritual with a physician and their team. And they come in on a regular basis. They're engaged in treatment.

This is in comparison to the response rate for usual care. Remember, from IMPACT and PROSPECT, the response rates at 12 months, and at four months for the PROSPECT project, was only 16% to 19%. So again, outcome really seems to depend more on the process of care, getting engaged in treatment, than on a specific drug.

That being said, there is an updated pharmacotherapy algorithm that came out of a Canadian subgroup of the Canadian Psychiatric Association that I think is very intelligent that I share with my fellows and trainees and recommend that people follow. It makes a lot of sense.

But again, it tries to be evidence based, but it's also evidence informed. And that's OK because we have to take data from younger adults and extrapolate it to older adults because we don't have all the RCT evidence to support it. But I like to follow this.

Being polite, diplomatic Canadians, they provide both the majority consensus and a minority alternative. And their recommendation is to start with escitalopram. And the alternatives are sertraline and duloxetine. The dosing strategies are really to get to the same top FDA-approved dose as for younger adults but to start slower if somebody is frail. But really, there's no dosing adjustments. I always try to push to the tolerated dose.

Step two for minimal or non-responses is switch to duloxetine. This is a bit of a shift from the 2001 and 2006 guidelines because there is RCT evidence that supports the duloxetine as superior to placebo and also because duloxetine is approved for so many chronic, painful conditions in older adults. And pain is such a prevalent condition in late life.

Step three for minimal or no response is to switch to nortriptyline, which I didn't include on that previous slide. But there is evidence that it's superior to placebo and works and is safe in older adults. And the alternative is bupropion, but there's data lacking this support. But we know that it's useful.

Step two to three for partial response is to augment the antidepressant with lithium. We know that lithium can be safely used in many older adults. And it's the only augmentation agent that has replicated evidence as an effective augmentation treatment for older adults with depression. Or use an atypical antipsychotic, and I'm going to share with you some data describing use of an atypical antipsychotic as an augmentation agent.

The duration of each step should be six weeks, or it can be shortened to four weeks if patients are showing absolutely no response by three to four weeks. But the consensus is to initiate only one medication at a time to avoid premature changes and to be circumspect about new medications for which rare adverse events may not yet have been recognized.

So let's talk about the Incomplete Response in Late-Life Depression-- Getting to Remission, the IRL-GRey project. And the overall goal of this study was to examine the efficacy and the tolerability of aripiprazole augmentation for older adults with treatment-resistant depression.

So the inclusion criteria was age 60 or older. They met our criteria for major depressive disorder, both early and late onset. They couldn't be demented because we didn't want to expose patients to aripiprazole because of the FDA black box warning about the use of atypical antipsychotics in dementia. And they couldn't currently be abusing a substance.

So let me walk you through the study. And there were three phases. Phase three was open label. Let's just look at phase one and phase two. So phase one was a 12-week, open-label study using venlafaxine up to 300 milligrams a day. And we wanted to prospectively determine treatment non-response.

So nonresponders to the venlafaxine then moved on to step two. And those patients were then augmented with aripiprazole or with placebo. And we dosed the aripiprazole at 2 milligrams up to 15 milligrams a day. And this was for another 12 weeks.

These are the baseline characteristics of patients when they came into phase two of the study right before augmentation with aripiprazole or placebo. I've highlighted just a couple of characteristics that I think are of interest. In general, not an especially old group of patients. They were in their mid-60s. Their illness burden was moderate. They had, on average, four to five chronic medical conditions, about average for this group of patients.

This was a highly anxious group of patients. So 40% of them were prescribed benzodiazepines before coming into the study. And they actually wanted to continue them. We tried to taper them off. The majority of them had a recurrent form of the depression. 3/4 of them had recurrent depression. Many of them had been depressed on and off since middle age, since their 30s or 40s. And the duration of the current episode prior to coming into the study was, on average, two years-- so a pretty sick group of patients.

And our two efficacy outcomes were depression improvement. And we defined that using the Montgomery-Asberg Depression Rating Scale. And we define remission as a score of 10 or less at two consecutive visits. And we also were interested in reduction in suicidal ideation.

And our reason for looking at suicidal ideation is because suicide is such a concern in older adults and, also, because we were worried that aripiprazole may increase rates of akathisia. So akathisia is a sense of subjective restlessness and disease and anxiety that has been associated with increased rates of suicidal ideation and behavior. So we wanted to show that this was not a contributor to suicidal ideation.

So in terms of efficacy results, just look at the left side of the slide. This is our rates of remission for patients augmented with aripiprazole compared to placebo. So 44% of those who received aripiprazole augmentation remitted compared to only 29% of those who received placebo.

And again, another way to interpret these data is to look at the number needed to treat. So the number needed to treat was 6.6, meaning we only had to expose a little more than six patients to augmentation with aripiprazole for one of them to remit. So put this into perspective.

The number needed to treat for atypical antipsychotics for treatment-resistant depression in younger adults is nine. And a higher number needed to treat is worse. And the number needed to treat is 13 for the overall efficacy of short-term pharmacotherapy of late-life depression, which really suggests that this is a pretty effective augmentation strategy.

So in terms of reducing suicidal ideation, about one third of the participants had suicidal ideation at the start of the augmentation phase. So again, this was a pretty ill group of patients. But suicidal ideation resolved in 3/4 of those patients who received aripiprazole augmentation compared to less than 50% of those who received placebo.

Well, you can't interpret the clinical efficacy outcomes of a clinical trial without looking at safety and tolerability. So let's first look at serious adverse events and adverse events. So there was no difference between aripiprazole and placebo for serious adverse events. There was no difference in the number of adverse events leading to discontinuation of the study medication.

So this is an important outcome. More people didn't stop the aripiprazole because they couldn't tolerate it compared to the placebo group. There was no difference in emergent suicidal ideation between the two groups. There was one suicide in the study. And that patient had been receiving aripiprazole.

This was a fellow at the Toronto site who jumped off of his balcony. But we determined it wasn't related to study participation or to akathisia. He had had numerous suicide attempts in the past, and this was just a tragic outcome. There was no effect on cardiac conduction parameters either. So from a cardiac standpoint, there was no negative effects.

Well, we also looked at extrapyramidal symptoms. Since this is an atypical antipsychotic, this is an important safety parameter to consider. And we measured akathisia. We measured Parkinsonism, so tremor and stiffness. And we measured tardive dyskinesia, which is a delayed-onset movement disorder, an involuntary movement that can occur after exposure to an antipsychotic.

And what we observed is that, yes, patients who received aripiprazole had higher rates of akathisia. So the rates of akathisia was about 26% compared to 12% for those receiving placebo. But in general, the akathisia was mild in severity, as you can see on the next row down. And we could usually manage this with a dose reduction.

In terms of Parkinsonism, again, higher rates of Parkinsonism in patients who received aripiprazole compared to those who received the placebo group, the placebo intervention, but, again, didn't contribute to early study discontinuation or stopping the medication. And it didn't increase the risk of falls.

And finally, there was no difference in terms of the incidence of tardive dyskinesia. But we only observed patients for out to 24 weeks. So I would caution people that this is still a concern that needs to be examined further.

So the other main tolerability and safety outcome that we looked at is cardiometabolic. And this is a concern for patients and clinicians when they start psychiatric medicines. They want to know, is this going to make me fat? So we looked at adiposity, so fat gain, as well as change in weight.

And if we look at the right side of this slide here first, this is the change in weight. The y-axis is weight change. The x-axis is the weight in kilograms at randomization. The line, the dotted line, at zero is the reference line. And above that means a weight increase. Below that means a weight loss.

And, yes, patients who received aripiprazole did gain a little bit more weight-- on average, a little less than 2 kilograms over the course of those 12 weeks. So they didn't blow up. There was not a tremendous increase in weight, but they did gain more weight than those receiving placebo.

However, if we look at the left side of this slide here, total change in body fat, and we measured this with DEXA scans. So the zero with the dotted line there is the reference line. Above that is an increase in fat. Below that is a decrease in fat. And in general, there was no increase in total fat for those who received aripiprazole compared to those who received placebo.

So only 30% of the weight increase in those who gained weight who received aripiprazole was due to fat gain. So I don't really know where the rest of this weight came from. It could have been that the patients were depressed. We got their depression better. They were eating better. And they were gaining muscle mass. It could have been that they were retaining fluid. But the good news is they weren't accumulating toxic fat cells.

So in conclusions for short-term efficacy and safety, it does seem to be efficacious for treatment-resistant, late-life depression. There's a higher remission rate and more reduction of depressive symptoms and a greater decrease in suicidal ideation. Aripiprazole was associated with increased rates of akathisia, which in general was mild, and Parkinsonism as well as tremor. But there was no increased rate of tardive dyskinesia over the course of these 24 weeks of follow up.

Over the short term, it didn't induce cardiometabolic risk. So there was some weight gain, but it wasn't tremendous. And there was no increase in fat. And there was no QTC prolongation.

But the question is, who benefits most? And where does aripiprazole belong in a treatment algorithm? So, and I have one minute left. I'm almost done.

So I want to share with you just a pearl about whether you should augment or switch. So I would suggest that after six weeks at a therapeutic dose, you consider augmenting and make this part of your predetermined algorithm with your preselected group of medications. So if somebody has at least a 50% improvement on a PHQ-9 score-- because now you're all going to be using measurement-based care-- or the patient reports clinically significant improvement in depression or associated symptom, and they're also a low-fall risk, and they have low polypharmacy, then I would augment. I would switch if they had a less than 50% improvement on the PHQ-9 or they report no difference.

So I want to wrap up with just a very brief introduction to an ongoing study that we have now because people want to know about what's cutting edge and what's coming on the pike for advances in treatment-resistant depression. So the OPTIMUM study hopes to answer a simple question because we know that 55% to 81% of older adults with major depressive disorder fail to remit with a selective serotonin reuptake inhibitor or a serotonin norepinephrine reuptake inhibitor.

And when older adults don't respond, what should primary care doctors do? What should be the next step in treatment? Should we switch? Or should we augment?

So this is a five-site study with Pittsburgh, UCLA, Toronto, Columbia, and Washington University in St. Louis. And we're recruiting 1,500 people across North America with treatment-resistant depression into this project, 300 here in Pittsburgh. So this is going to be the definitive study of algorithmic approaches to get people with treatment-resistant depression well.

And we've learned from these other studies that I've shared with you. So we're using a collaborative care approach where geriatric psychiatrists provide recommendations based on a predetermined algorithm. Assessors or depression care managers measure outcomes and support primary care physicians, usually by phone or the electronic medical record. Patients stay with their provider, and the provider prescribes medication.

It's a simple, real-world design. And we're hoping to fill in some of these gaps that are missing from the evidence base. So we're testing if we should augment with aripiprazole, augment with Wellbutrin or bupropion, or switch to bupropion-- common questions that we all encounter in the clinic. This is for 10 weeks. If patients don't respond at the end of those 10 weeks, we're testing whether we should augment with lithium or switch to nortriptyline.

Patients can do this entire study by phone. In Oakland, if they're nearby, or we do home visits. We provide decision support. We communicate to the PCP. And because of the tremendous size of this study, again, 1,500 people coming into this project, we'll be able to determine which treatment works best for which kind of patient. So we can do subgroup analysis based on age, medical comordibity, and cognitive status.

So in summary, I would say that late-life depression can be effectively treated. I think that we'll get superior outcomes by following a systematic approach and that success requires persistence. Aripiprazole augmentation appears to be effective and safe. But its position in algorithmic care still is not yet established.

And I think that the OPTIMUM study, which will be done in about two and a half years, may be the definitive study of real-world treatment for late-life, treatment-resistant depression. And finally, again, we can't give in to therapeutic nihilism with these patients because we can get these patients better. So I'm going to stop here. And I want to thank the organizers and you all for your attention.