DR. NADA EL HUSSEINI: I will be talking about behavioral changes and depression post-stroke. And I think that's important because it's very common. And because, as a neurologist and a stroke neurologist, we do need to pay attention to these sometimes unmeasured, or not immediately measured, outcomes. Especially in the hospital, we are focusing more on the motor recovery and how to go home. But this is something that's very common, and prevalent, and very important for patients. And that, as you will see, will affect stroke recovery quite a bit.

So I don't have any financial disclosures. My only disclosure is that I'm not a psychiatrist. So I'll be talking from the perspective of a stroke neurologist who takes care of these issues.

The behavioral changes after stroke can be divided into the following. Mood disorders, depression being the most common-- mania is also possible-- anxiety disorders, pseudobulbar affect. Also, patients can have behavioral changes because of cognitive changes. So dementia-- vascular dementia-- can lead to behavioral changes. I will not be really talking much about cognitive changes today. It's a talk on it's own.

Personality changes. And they don't need to necessarily fit into a disorder, but I see a lot of patients who tell me-- or their partners with tell me-- well, they just changed. They are not depressed, they are not anxious, they are apathetic. They just don't care anymore. Or they became impatient. So you can see, also, personality changes. Again, the highlighted ones, the mood disorder, anxiety disorder, and pseudobulbar affect is what we're going to focus on today.

So I'm going to start with post-stroke anxiety, and I'm going to leave the depression till the very end. It's going to be the largest chunk of this talk because it's the most common disorder. But starting with anxiety. As you all know stroke is a threatening event. So patients or stroke survivors are mostly concerned about loss of function, loss of independence, death. Even if they have recovered fully. And I see this-- and that's well-documented in the literature too-- that this can happen quite often, even after TIA. So it doesn't necessarily need to be related to disability. Patients can recover and still be very-- because it hit them suddenly-- very concerned about, are they going to have another stroke. And if they do, what will the outcome be?

The frequency of anxiety is, in the literature, about 20% to 30% following a stroke. It is associated with decreased ability to perform ADLs. There was a three year longitudinal study in 1996, published in Stroke, of 80 patients. The prevalence of generalized anxiety disorder, between zero and three months after a stroke, was about 28%. And only 23% of these patients recovered in one year. And the prevalence at three years decreased, but still was pretty high at 19%. There was high association and co-morbidity with major depression. So patients can have anxiety as well as depression. And it was associated with dependence in ADLs and reduced social network.

There was another study in 149 stroke survivors in Sweden, assessed at 20 months-- so close to two years post-stroke-- compared to the general population matched for age and sex. And they found 27% had anxiety compared to 8% in the general population. So you can see that in the stroke cohort there was much more anxiety. The generalized anxiety disorder was associated with stroke, female sex, and also co-morbid depression.

And here I'm mentioning a systematic review of predictors. So what are characteristics that can increase the risk of anxiety? And that systematic review looked at all the studies published in the English literature, up to may 2014, and it included 10,432 patients. The main predictor, again, were pre-stroke depression, stroke severity, early anxiety after stroke, and cognitive impairment.

In terms of treatment, there is nothing specific about anxiety after stroke. There are no randomized controlled trials. Typically, the treatment of anxiety is SSRI, Buspierone. and we try to avoid chronic use of benzodiazepine. So that's not something that we like to use.

So now I'll move to post-stroke mania. And this MRI is actually from one of my patients who developed post-stroke mania. As you see, it's a right parietal stroke. He developed the mania about one year after his stroke. He was in his 60s, and had no previous history of psychiatric disorders. The frequency is less than 1%. Not common. It can happen though. And it is correlated with right hemispherical lesions similar to what this gentleman has.

It is thought to be due to dysfunction in the ventral limbic circuit that involves the right orbital frontal basal temporal cortices, dorsomedial thalemic nucleus, and head of the caudate nucleus. It is associated with premorbid depression, family history of mood disorder.

Again, here there are no randomized controlled trials for treatments, specifically in mania after stroke. But the general treatment is the traditional treatment, lithium, which we try to avoid in stroke patients. Not really contraindicated, but we try to avoid it. Valproic acid, carbamazepine are more commonly used. Clonidine, neuroleptics, and benzodiazepines.

There was a systematic review, actually, about post-stroke mania. And that was published in 2011. It included only 74 cases. So you see, again, not a lot of cases published in the literature about that. They are mostly case reports, case series, cohorts. No randomized controlled trials. And they were published-- these are all the cases that were published between 1960 and 2010.

The temporal relationship between the stroke and the development of mania was only established in 49 of these cases. And 58% occurred immediately after stroke, 23% during the first month after a stroke, and 23% after the first month up to two years. Again, in the patient that I mentioned, it was a year after his stroke. It is most frequent in males, right cerebral infarct, and based on this systematic review there was no association with personal or family history of psychiatric disorder. The most common symptoms were elevated mood, increased rate or amount of speech, insomnia, and agitation. And the patients that I mentioned had all of them, and unfortunately it was so severe that he had to be admitted to the psych ward.

Now I'll move to pseudobulbar affect. The definition of pseudobulbar affect is frequent and easily provoked spells of emotions-- such as crying or laughing for several minutes-- that may be inappropriate. So sometimes it's appropriately something that's funny, but people would just not be able to stop from laughing for minutes. So it's excessive reaction. Or sometimes they laugh at a really wrong moment, like during a funeral. And crying with pseudobulbar affect is actually more common than laughing. Because of crying, pseudobulbar affect may be mistaken for depression. But what differentiates it is that typically the person doesn't necessarily feel sad. Doesn't have the vegetative symptoms of depression. However, depression is highly comorbid. So you can have depression and pseudobulbar affect in the same patient.

The frequency is about 10% to 15% following stroke. It may occur-- it's not really specific to stroke, pseudobulbar affect-- can happen with other neurologic conditions including ALS, multiple sclerosis, traumatic brain injury, brain tumors, Alzheimer's, Parkinson's disease. Severe symptoms can cause embarrassment, social isolation, anxiety, depression.

We think that pseudobulbar affect is caused by a disconnect between the frontal lobe-- so here I have this small picture, and here-- the frontal lobe, the cerebellum, and the brain stem. So having lesions around and affecting this pathway caused this disinhibition syndrome.

So other words that you may have heard for pseudobulbar affect are emotional incontinence or lability. It involves glubamatergic and serotonin pathways. The traditional treatments, before Nuedexta, where SSRIs, TCAs. Amantidine, and dopaminergic medications were sometimes used, but not really very effective.

And then Nuedexta came-- which is a combination of dextromethorphan, 20 milligrams, and quinidine, 10 milligrams-- and that was FDA approved in October 2010. It works by-- so the dextromethorphan, as you may know, it's an antitussive medication-- it inhibits the glutamaturgic neurotransmission. And quinidine blocks its hepatic metabolism, so its level increases in the blood, and can actually cross the blood brain barrier. It is effective. When it was compared, and the FDA approved it, it was compared against placebo. It seems to be effective. It was never compared to anti-depressant medications. And it is contraindicated in patients with prolonged QT interval, complete heart block, history of torsade de pointe, or heart failure.

So now I'll move to the post-stroke depression. And I'm going to start with a case study, also of a real patient. She had her stroke in 2013, in December. She was 44 at that time, has history of migraine, and depression. Presented with dysarthria and left sided weakness. And you see here, her scan. It's all kind of the right parietal and medial temporal infarct. Her NIH stroke scale was three, she did not get TPA, was started on aspirin and Lipitor, and she had a history of depression. She was on Lexapro(escitalopram), 10 milligrams, that was continued.

She was seen in the clinic a few months later, and she had residual symptoms of left hand weakness, trouble writing, coordination deficits which worse worsen when she's tired, and when she has headaches she was having daily headaches. She was concerned about her memory, and she was having trouble sleeping. Her MOCA was 28-- so the Montreal Cognitive Assessment was 28-- so within normal. And the PHQ-9-- which we will talk about, it's a depression screen-- was 13, indicating moderate depression.

The plan during that clinic visit was to increase the Lexapro dose to 20 milligrams, to help stabilize her depression. She was referred to speech cognitive therapy, and disability paperwork were filled for her.

A few months later, she was seen again in clinic. Her Modified Rankin score was a two. So she had not completely recovered, still had symptoms, but was still able to do most of her ADLs. She continued to have some tingling, weakness, occasional spasms on her left side. She would get tired easily, and was still concerned about cognitive challenges even though her MOCA is 28. So that doesn't rule out that people can't have subtle cognitive changes. She had not returned to driving, not returned to work-- she does office work-- and since Lexapro increased she felt that her mood was much improved. And she was planning to go to work within a month at a reduced schedule.

In August, her Modified Rankin score was even better. She was back to work, she was driving, started the full work schedule, she denied any depression or anxiety. And then, fast forward now to January, 2015. So that's a year after her stroke. She had urgent evaluation for worsening left sided weakness, a feeling of being off balance, cognitive changes that have been constant over the past couple of weeks. It was very tearful. She was very worried. Worried about having another stroke. And she could hardly talk without crying, was having night sweats, was losing weight. Given her cognitive memory challenges she was referred to neuropsychology. Her disability paperwork were filled again. An MRI was done that did not show any new strokes.

She saw her primary care physician, and during that time her Lexapro was continued and Wellbutrin was added. And I saw her in May of 2016, so that's now almost two years and a half after her stroke. She was working part time, feeling much less stressed, was working in a different environment. She feels that the depression was better, and in retrospect she felt that going back to her previous job was the most stressful thing. She just decompensated. And she reports that the medication was-- when I asked her, what do you think has actually helped to get you through this-- said really the medications and her faith. As well as coming to terms with the new limitations, and adjusting her job to what she can actually do without feeling overwhelmed. Her PHQ-9 was three, so that indicates very mild depressive symptoms. Not clinically significant.

So here are the questions that I would like to address, and we will address them during this talk. First, does she meet the criteria for post-stroke depression? She had a previous history of depression. Does she actually have post-stroke depression? What are the risk factors for her to develop depression? Is the course of depression in this patient typical? To present a year later. To get worse that long after a stroke. And did her depression increase health care utilization, and could depression have been prevented in this patient?

So the definition of post-stroke depression is depression occurring in the context of a clinically apparent stroke. As opposed to silent cerebral vascular disease. There's really no time limit. It doesn't define if it's one year, five years, two years. The gold standard is the DSM. Right now we're at DSM five. And there is still controversy about how it differs, in terms of pathophysiology and even characteristics, from endogenous depression. Both its phenotype and neuroanatomical basis.

So there are several studies here that looked at symptoms. The question was, do symptoms of depression in stroke patients differ from patients who have depression but no stroke? And there is no consensus about that. Some studies here. The first is depressed patients with stroke exhibit more loss of interest, psychomotor retardation, gastrointestinal complaints as compared to depressed patients with MI for example. With myocardial infarction. More anxiety symptoms in patients with stroke than patients with spinal cord injury and myocardial infarction. And these two studies did not find any specific features when compared to depression in the general population.

There are many depression scales that are used, and that have been validated for post-stroke depression. These are some of them. The Beck depression, the CES-D, the Geriatric Depression Scale, the Hamilton Depression Scale. There is still no widely approved optimal screening for post-stroke depression. There are some stroke specific scales. They have not gained much traction though. They are not very widely used, but they exist. The post-stroke depression scale, and aphasic depression rating scale.

The prevalence rate differ according to the assessment. And here, that's an interesting finding. Is that the lowest rates are with the DSM, which is our gold standard. And the highest rate is when you used a caregiver rating, when the caregivers comment, do you think that your loved one is depressed. And when they comment about it it's actually three-fold higher than what the DSM would show. And an interesting study showed that actually, caregiver ratings correlate with a caregiver depression score.

So here, there was a meta-analysis about diagnosis and screening tools that was published in 2014. And that included 2,907 participants. Again, here you can see sensitivity, specificity, positive predictive value, negative predictive value about each of these. I must say, that the first scientific advisory from the American Heart Association is going to be published very soon. About post-stroke depression. And they did look in the advisory at this, and you will see what they recommend, hopefully, when that paper comes out very soon.

But it seems like there is some favor for the PHQ-9. Because it's easy to administer. I do it in my clinic. It's a self administered questionnaire, I explain to the patient how to do it, if they need more help then I sit and guide them through it. And it seems like it has good negative predictive value, and good enough sensitivity and positive predictive value. And compared to the other ones, here, you see that it has the best negative predictive value. So that means that if they score negative on it they most likely don't have depression.

This is what the PHQ-9 is. It's a series of these nine questions, which are taken from the DSM criteria for depression. You ask them, over the past two weeks how often have you had any of these symptoms. Not at all, several days, more than half of the days, nearly every day. They circle the one that matches best how they feel. You calculate it at the end. If it's 10 or more, it's usually a clinically significant result. And this is widely available. You can Google it and print it out.

So again, depression is the most commonly occurring psychiatry disorder after a stroke. In terms of the frequency, there was a meta analysis of 51 studies before 2004 which confirmed that the overall frequency is about 33%. The meta analysis-- another one was done by a different person-- in 2011 still showing about 29%. The incidence in the first year after a stroke is 10% to 15%. So these are patients who are having a new onset of depression. About 10% to 15%. And the cumulative incidence, within five years, is 39 to 52. This is 15% to 50% of patients, with post-stroke depression within three months of stroke, recover one year later.

So people can recover, and I'm going to show you a study where it shows that people can recover even without any treatment. It's not impossible. And to give you an idea how this compares to the general population, for example in 2008, US population aged 18 and older had 6.7% of major depression. So much higher in the stroke population.

Again, this is just another kind of pictorial way to look here from that meta analysis in 2005. To see that most studies published showed that prevalence, regardless if you look at long term, medium term, or acute phase, about 33%. And here when it's stratified by study setting, population, the hospital, or rehab setting.

There was also the Framingham study that actually compared patients with stroke to controls matched for age and sex. And also 38% of stroke survivors were depressed at six months, as compared to only 10% of controls. Now, you're going to see in these studies that there is a lot of variation in terms of the point prevalence. And this is because of multiple-- first, it really depends on what scale is used in the study. And also, there's a questionable reliability of self-ratings in acute stroke population due to aphasia, anosognosia, or cognitive impairment. And there are multiple diagnostic confounders such as anxiety, post-traumatic stress disorder, fatigue, and apathy.

Now what's the natural history? There are two population based studies, one hospital based, and four rehab. Over all there seems to be a constant frequency of depression in the total stroke population after the first year after a stroke. So at any one time, if you have a cohort, and you're sampling it to see how many of these patients are depressed, you're going to get somewhere around 30%. Because some people recover, and some people have new onset depression within that year.

Here in a longitudinal study of 224 patients, long-term post-stroke depressive symptoms were highly predictable at six months. So depression at six months or three months does predict long term depression. Even though it doesn't mean that, certainly, the stroke survivor will be depressed forever.

Post-stroke depression was present at six months, one year, and three years, in that particular cohort, in 12.2% of patients. And of the patients without post-stroke depression, six months post-stroke, only 3% had post-stroke depression at three years. So it certainly seems like early onset, or depression in the first year, predicts long term. Again, it's not impossible that patients can develop it after the first year.

Here is one paper that we published in Stroke in 2012. And in this study we looked at depression and anti-depressant use after stroke and transient ischemic attack. And we used a Get With The Guideline cohort. That's part of what was an ongoing study called the AVAIL database. We included 2,400. We started here and we ended up with 1,450 stroke patients, and then 397 TIA patients after excluding people who did not have enough information to get the study. And we used the PHQ-8 for that study. So that difference between PHQ-8 and PHQ-9 is that the PHQ-8 lacks the suicidality question. And that, sometimes, is used in databases where if the patient answers yes for suicide, you don't really have a means to address this. So you just do the PHQ-8. They actually correlate pretty well.

And this is what we found. We tracked pretty much every single person in the cohort. To see how they started, and how they ended. And what we found is that new onset depression occurred and 8.7% of stroke patients versus 6.2% of TIA patients. So that was one of the interesting results. There was no statistical significance between the two. So in this particular study what we found is that in TIA, patients were as likely to have new onset depression.

Now the results may be due to the fact that our stroke patients in this study had minor strokes. Their NIH Stroke Scales were actually low. So that may be one explanation, but it's not the only study that showed that the risk of stroke and anxiety after TIAs is high, and higher than the general population.

So what we also learned is that the prevalence of depression over the year following stroke and TIA was constant. So similar to other observations from other studies. And among patients who were depressed at both three and 12 months, 67.9% of stroke, 70% of TIA patients were actually not using antidepressants at either time points. And among those using antidepressants the majority were not scoring depressed. So that may indicate that these patients were either overmedicated, or that they actually were responding appropriately to their drug.

And depression at three months has resolved by 12 months in 44.4% percent of stroke, and 48.8% of TIA patients without the use of antidepressants. And persistent depression despite antidepressant use, at both time points, really occurred in only a minority of stroke patients. So that really would suggest that, perhaps, if we identify and treat depression after stroke, it's not as resistant as we think. It can actually respond to treatment. Because only 1.9% and 1.5% were actually depressed despite taking their anti-depressant medication.

So now, moving on to pathophysiology. It is still really not clear-- I mean, the general reaction is, who wouldn't be depressed after a stroke. How can you not be depressed? But I think there are some indications that it may be beyond that. And one of these indications-- we already mentioned it-- patients can be depressed after a TIA. Again, for maybe different reasons. They just had a major life event, even though they were back to normal. And they have anxiety, and they can get depressed as well. But it may be that there is some real biological mechanism that causes depression. Just like we saw that it causes mania and pseudobulbar affect.

So the two major theories, again, reactional psychosocial and stress mechanisms. So that may respond better to psychotherapy and social support. Or that it's a biological mechanism that ischemic insults directly affect neural circuits involved in mood regulation. And that may respond better to pharmacological therapy. So that's maybe why it's important to try to differentiate. But so far we don't really have a consensus.

Some studies show that-- actually, this pans out in a lot of studies, even though we said that depression happens after a TIA-- still one of the predictors of depression is disability. So the reactional psychosocial and stress theory can pan out there. And also, risk factors for post-stroke depression are a major life event before stroke, previous history of major depression, and social isolation. So it's not always related to the actual lesion.

Things that indicate or point to the fact that it may be really more biological factors. That disruption of cortico-striatal-pallidal-thalamic cortical projections. The lesion location, and there are lots of studies about that, and lots of meta analysis. The current consensus is that there's really no association, no definite association, between the lesion location and post-stroke depression. It used to be-- and Dr. Robinson had published a lot of that-- that we used to think that it's mostly left sided lesions. At this time, after more meta analysis, it doesn't seem to pan out. So there's still no definite association between post-stroke depression--

The genetic susceptibility. So there are some smaller studies talking about serotonin transporter genes, methylation status, and neurotropic factor methylation status, interlukin4, interleukin-10, genotypes. And whether these predispose patients have more post-stroke depressions after a stroke.

Inflammation, alterations in neurotransmitters. There are studies about cerebral blood flow, cortisol levels, brain amygdala volume as something that predicts post-stroke depression.

Other things that can indicate that this is really biological is that depression can occur in patients who have anosognosia. Meaning people who don't even realize they've had the stroke-- it's usually with right side stroke-- they can still be depressed. Depression also was more frequent in stroke patients than orthopedic patients with the same level of physical disability. Post-stroke depressive like symptoms are also noted in several animal models. And late onset depression patients who don't really have sudden onset of strokes, but who have white matter disease, and silent infarcts. As we all know, it's certainly associated with late onset depression too. And as we saw, also, even in patients who have TIAs and minor strokes there was an increased risk of depression.

At this point, it seems what it explains it is similar to what explains depression in the general population. It seems to be a psychosocial and biological basis.

So now, we move forward to predictors of post-stroke depression. So when you're seeing patients in clinic, or in the hospital, what are some things that may point to the fact that this patient is more at risk for having this complication?

Cognitive impairment-- so this is based on multiple studies and reviews, that I put these here. Cognitive impairment, certainly, pans out. It's well associated with depression. Personal history of depression. So a previous history of depression before the stroke increases the risk of depression after the stroke. Physical disability, and stroke severity. These are well associated with post-stroke depression. Other studies show that social factors. Living alone, lack of social support, social isolation, and anxiety after a stroke. And then there are mixed results on age. In our study we found that younger age was actually associated with increased risk. But not all studies have found the same thing. The education level-- less education-- female sex, and the stroke subtype.

So again, this is what we found in the study that I presented earlier, that was published in Stroke. That younger patients had actually less risk of depression at 12 months, and less risk for persistent-- I'm sorry, younger patients had more. So here, as you go up in age you had less risk of depression at 12 months and persistent depression.

And then we looked at work status at three months. And people who were working at home, not by choice-- who had to leave their work without choosing that-- were at also a higher risk for having depression. So if they were still working, or they were home by choice, they were less likely to be depressed. Depression at three months certainly was a strong predictor for depression at 12 months. And then the Modified Rankin Score. For each unit increase in the Modified Rankin Score, there was an increased risk of depression. Both at 12 months, and for persistent depression.

And now, this is another interesting question. As you may know, the Joint Commission does require that all hospitals actually screen for depression, after a stroke, while in the hospital. And this is something that we're trying to figure out. What's the best way to deal with that? Again, we don't have across the board screening tools to tell you, this is the screening you need to use in the hospital. And then the question is, how does the result correlate to future depression?

So this is based on a small study that we did to look at a subanalysis of the Q5 the EQ-5D-3L, which is the depression and anxiety portion of that health assessment questionnaire. And also, we looked at the pre-hospital history of depression. And based on this small study-- we had 124 patients for the first analysis, and 69, so not a huge study, but not too small either-- what we found here is that pre-stroke history of depression certainly predicted three month depression. That is not a surprising result. We mentioned already that that's kind of a well known, established factor. But also, we found-- based on this small study-- that in-hospital assessment that indicated depression or anxiety did correlate with three month. That's again, a small study. We're doing more of that to determine what to do.

However, it seems like if you're going to have a screening mechanism in the hospital, that the best way to actually get something out of it is to have a pathway. Like any screening. If you do a screening, and don't do anything about it, it's not likely to help.

There are some interesting racial and ethnic disparities in the detection of post-stroke depression. And here, whether it's the detection, or whether patients actually have less depression, is unknown. But based on a national cohort from the VA of stroke patients with acute stroke in 2001 that included 5,825 patients-- 66% were white, 22% black, 7% Hispanic, 6% other racial ethnic categories. And post-stroke depression was defined as a depression diagnosis that was documented in the medical record, or if the patient was on antidepressants. 39% in this cohort had post-stroke depression, based on this definition.

And after adjusting for sociodemographic and clinical factors white non-Hispanic patients were more likely diagnosed with post-stroke depression, within one year post-stroke, compared to blacks. Which the odds ratio was 0.57. So again, it is unclear if this is due to differences in endorsement by the patients, or in the symptom recognition by providers. But the results are similar to findings in the depression literature in general.

So now, how does post-stroke depression impact stroke outcomes? Let's see how much time-- OK. So the AHA there was already had a scientific statement about how depression effects outcomes after acute MI. And that's already since 2014, it came as a scientific statement saying that depression should be elevated to the status of a risk factor for adverse medical outcomes in patients with acute MI.

So hopefully we'll have something similar in stroke to establish it. But there are multiple studies that suggest that post-stroke depression is actually worse in outcomes. One of the outcomes is functional outcome. So post-stroke depression may impair functional outcome by decreasing neuroplasticity, limiting participation in rehab, decreasing physical, cognitive, and social function. There was a systematic review that found that post-stroke depression is indeed associated with worse functional outcome. However, both depressed and non-depressed groups showed equal improvement over baseline and ADL.

So even though they may improve similarly, because they are starting at a worse point they will likely end up at a worse point too. So at each point you're evaluating the functional outcome, it seems like a patient with stroke would have a worse outcome. But they may still improve. It doesn't mean that they will not. But the end point, if they are still depressed, would still be that it's worse function.

Now is it associated with recurrent stroke? It seems like it is. There was a multi-center prospective study in China of 2,306 patients, and there was a higher rate of stroke recurrence among those who had depression. The odds ratio was 1.49. Is it associated with higher health care utilization? It seems like it is. There more hospitalizations, outpatient visits, longer hospital stays. And more inpatient hospital days, and-- again, here another study showing the same thing-- and outpatient visits.

Is it associated with mortality? And it seems like it is as well. There was a meta analysis in 2012 that showed that people who had post-stroke depression had a higher hazard ratio for mortality. 1.52. And here, patients with depression were 3.4 times more likely to have died during the follow up than non-depressed patients. Patients who had depression, and few social contacts, over 10 years were actually 90% likely to die.

And here, there's another VA study of 51,119 patients, from 1990 to 1998. And both post-stroke depression and mental health diagnoses independently increase the hazard for death. Even after other chronic conditions and stroke severity were controlled for. So it seems like it is well established that it is associated with worse functional outcome, increased mortality, increased health care utilization.

Now, how about suicidality? Stroke is also an increased risk for suicidality. Certainly the mechanism of death is mostly not through suicide, but there have been several studies talking about suicidality in patients who have post-stroke depression and stroke. And there was a study of 177 patients within four days of acute stroke. 15% had suicidal thoughts. Suicidal thoughts were more common in patients with lower educational levels, diabetes, and acute depression.

A study in Northern Finland, between 1988 and 2007, showed that pre-stroke depression increased the hazards of suicide after stroke up to 2.2 fold. Compared to stroke without lifetime depression. And the highest risk of suicide, after a stroke, was up to two years after. A study in Denmark-- so a lot of the studies are from Denmark and Sweden and Finland-- so between 1979 and 1993 it seems like stroke doubled the risk of suicide. And the greatest risk of suicide is among younger patients. And greatest, again, was within the first, one study shows, two years, and one shows five years.

This study was published here in Neurology in 2015, also from Sweden. A nationwide cohort study between 2001 and 2012 of 222,336 stroke patients. And there were 1,217 suicides, of which 260 were fatal, and that was double the rate of the general Swedish population. Again, the increased risk of suicide was higher with lower education or income, living alone, male sex, young age, severe stroke, and post-stroke depression. But suicide doesn't only occur in patients who endorse depression.

So now, treatment. There are some randomized controlled trials in post-stroke depression, and pretty much TCAs, nortriptiline and SSRIs seem to work. Just like in endogenous depression.

There was a systematic review in 2008 of 1,655 participants for 13 pharmaceutical suitable agents. No trials of ECT-- or electroconvulsive therapy. The results show that there seems to be benefit for pharmacotherapy. Obviously, more adverse events because you're taking a new drug. And they did analyze psychotherapy then, and they said there was no benefit. However, there were several randomized controlled studies, since that Cochrane review in 2008, that do suggest that psychosocial interventions may be useful. But these studies were limited because they did not exclude the use of anti-depressants.

Other treatment modalities that are being used in pilot studies. Transcranial magnetic stimulation, art therapy, ECT, exercise. Now there was a study here, by Dr. Williams in 2007, of a Care Management Program. Where-- it's called AIM, activate-initiate-monitor-- it was a randomized controlled trial of 180 patients. There was a care management strategy of a nurse care manager, supervised by study physicians, which is psychoeducational sessions to activate survivors and families to understand depression, accept treatment, initiate anti-depressant treatment, and monitor the treatment with scripted bi-monthly telephone calls.

The control was usual care with the same number of telephone sessions that focused only on recognition and monitoring of stroke symptoms and risk, without mentioning much about depression. And the remission was achieved-- so this is the Hamilton Depression Rating Score-- was achieved in 39% versus 28% favoring the intervention group.

So here, going back to our case, did the patient suffer from post-stroke depression? She did. Having a previous history of depression does not exclude the diagnosis of post-stroke depression. Actually, it is a risk factor. So in this patient, she had a previous history of depression. That's a risk factor for her to develop post-stroke depression. Cognitive impairment-- even though her MOCA, again, was 28-- she felt it, and the neuropsych assessment did actually reveal some impairment there. And possibly, young age. Again, in our study we found that young age is associated with post-stroke depression.

Now, is the course of depression in this patient typical to develop one year later? Again, based on the data that I just presented, yeah. It's not unusual. It can happen a year later. And the natural history of stroke depression is dynamic. Did depression increase health care utilization? As you saw, a year later she presented with more symptoms. That really did not have any MRI correlates, and once her depression was treated her symptoms resolved. So it seems like, yes, it did increase it here. And like you saw in studies, it is associated with increased health care utilization.

And in this patient, could depression have been prevented? Possibly-- hard to tell-- by early increase of anti-depressant medication. Again, there are studies-- I did not really address them, because they are still not a guideline in any way to start everybody on antidepressants-- however, we know now more and more, we're doing this-- especially with Prozac, based on the FLAME study-- for motor recovery sometimes. But in this particular patient, whether earlier increase of anti-depressant medication-- when she started mentioning these symptoms early on-- addressing her cognitive impairment early on, and adjusting her job early on to what she can actually do.

And then frequent follow up in this particular patient was appropriate. So for stroke patients, even though it's that acute event, and we see them three months later, the question is, how often do you see your stroke patients? Do you see them every year? I do because they can have issues. Years later they can still have issues. And so it's good that this patient had the appropriate follow up as well.

So the take home message is that behavioral changes following stroke are common. We mentioned depression being the most common of all. Mania, anxiety, pseudobulbar affect, personality change, and cognitive impairment. Depression occurs in about one third of stroke survivors at any one time. With a cumulative incidence of up to 50% over the first five years.

And the most consistent predictors of post-stroke depression include physical disability, stroke severity, history of depression, cognitive impairment.

Anti-depressant medications and psychosocial interventions seem to be effective in treating post-stroke depression. Post-stroke depression is associated with worse functional outcome, increased stroke recurrence, increased health care utilization, and increased mortality.

And more research is needed to determine whether screening for post-stroke depression-- and when to screen-- in conjunction with interventions improve stroke outcomes.

Based on everything that I said, I feel compelled to screen, and I do. I ask my patients in the hospital, as well as in the clinic, how they are feeling. And I ask about depression, and I often do the PHQ-9 as well, and address it. Now, do I always treat depression myself? It depends. It depends on their psychiatric history. If they are already on anti-depressant medication, have a history of bipolar, or of complicated depression, I do refer them to a psychiatrist. If they have not tried anything then I typically start the medication myself, and follow them up. So it really depends. And I have references here at the end for you.

That's all.

[APPLAUSE]