[MUSIC PLAYING]

FRED RUBIN: And we're going to talk about what's new in delirium over the past year. This is basically an update-- a literature review for the past year. I'm going to go relatively quickly, but everything is in your handout.

There we go-- no financial disclosures. And before talking about delirium specifically, I like to just remind us all that delirium is one of many bad things that happen to elderly patients under our noses, especially in the hospital environment. Iatrogenesis is disproportionately a burden carried by our elderly patients. And it happens that that exact same slide reflects the number of delirium publications that have been coming out in the literature over the past year or so. One of the references at the end is called hospitalelderlifeprogram.org, which has an annotated bibliography.

And that bibliography started out, a number of years ago, with about 200 citations. Currently, it has just over 3,000 citations. And it's wonderful, by the way. You can search it by topic, by author, by whatever you want. But there's a avalanche of new publications coming out in delirium, and I'm going to highlight what I think are the most important of them in the past year for you, right now.

These are some of the topics that we're going to quickly go over. But before we do, just a quick review of the basics of delirium to make sure that we're all on the same page. So delirium has a precise definition, and this is it. It's in the DSM-- diagnostic and Statistical Manual-- put out by the American Psychiatric Association.

And again, this and the next several slides are review for everybody here. But the key for what is delirium is that it's a disturbance in attention. The patient can't focus their concentration. It tends to come on acutely and fluctuates-- better, worse, better, worse, better during the day, better during the night. And, in addition to a concentration problem, there's a problem with cognition-- with their thinking. And the rest of it, you see.

There are diseases that mimic delirium, and here they are-- dementia, depression, and psychosis all have some similar features to delirium. I'm not going to go over this now. We know, from years of research, that not all of us are equally likely to become delirious. Some of us are much more likely than others.

And we divide the risk factors for delirium into predisposing factors and precipitating factors. Predisposing factors or those that the patient carries along with them, and here is the list of things that are predisposing factors-- I would point out that male sex happens to be one of those predisposing factors. I don't know why, but it's been shown. These are the precipitating factors-- and again, this is exactly what you would expect, the things that push a person into acute delirium, mostly acute medical illness.

This is the relationship between predisposing factors and precipitating factors. Let's see if the pointer works-- yes. Can you see that? OK. So if one has very few precipitating factors-- excuse me, if one has a lot of predisposing factors, it doesn't take much precipitating factors to push somebody into delirium. So it's sort of how close to the edge of the precipice is your patient standing, and then how big of a nudge do they get to knock them over?

There's nobody who can't become delirious. Every one of us has the ability to become delirious if we're stressed sufficiently. In terms of how we operationalize the definition of delirium at the bedside in our daily work, there's a number of instruments that are out there. But the one that is clearly the best, in my opinion, is called the CAM, the Confusion Assessment Method.

I'm sure this is familiar to all of you. It's these four criteria. And the sensitivity and specificity of the CAM are very high. This is an excellent bedside test. The CAM has been modified a number of times in 25 years or so since it was developed. The one that we mostly use at the bedside is either the short CAM, which is what I just showed you, or the 3D Cam, which is essentially the short CAM but made even easier.

If you go to the website I mentioned, hospitalelderlifeprogram.org, you can find not only all of these instruments, but also detailed instructions. There's user manuals for how to use the CAM-- how to use all of these things. You don't have to sort of wonder, am I doing it right? It's all written out there in great detail on that website, and it's freely available how to actually do it right.

An important modification of the CAM is the one at the bottom, the CAM-S. This is a research tool that we are not using at the bedside to take care of our patients. But it's increasingly clear that the severity and the duration of delirium predict the outcome. But if you don't measure the severity, then you're kind of winging it. Which is fine for clinical medicine, but for research studies, nowadays, if they're not measuring severity, it's not really state-of-the-art research.

Another new instrument that has just been published in the past year or so is called the DEL-B, which stands for Delirium Burden. We all know it's burdensome for patients families and nursing staff to take care of somebody with delirium, but now we have a way to quantify how burdensome is it anyway. And this is an overview of the DEL-B for a patient, at the top, and for a family caregiver, at the bottom. The C is caregiver.

So again, I'm not going to go through this in any detail, but you have the references if you want to go through it yourself. This is a research tool. But I show it to you because it's interesting, and nobody's really tried to quantify the burden of the pain of delirium prior to this.

Another new instrument for assessing delirium at the bedside that is very useful, and that I would recommend to all of us that we should be doing this, starting tomorrow, is the ultrabrief screen. This was published by Fick et all a couple of years ago, with an update just in the last couple months. It's two questions-- you say to the patient, can you say the months of the year backwards, and what's the day of the week right now?

And you can see, very sensitive if a patient cannot do those things. The follow-up study that was just published in the last couple months looked at, what if you only do months of the year backwards for six months versus 12 months? We're busy people. Maybe we don't have time to stand there for 12 months.

[LAUGHTER]

And so they looked at, does it actually make a difference? And it turns out, it does. And so you're supposed to do it for the whole 12 months.

Changing the subject from delirium instruments to what's new in thinking about what's going on in the brain of somebody who has delirium, there's a bunch of different models out there of what's going on in people's brains. This is an unreadable slide, but you've got the reference and you've got it in your handouts. This is slightly more readable.

These are the hypotheses for what's going on in people's brains in the left-most column. The one that gains the most traction is neuroinflammation. The classic example of that is shown here, especially post-op delirium. Theoretically, things that are anti-inflammatory might work. Although, so far, we have zero data to support that these things do work. But it's interesting to think about what's going on in somebody's brain, and I'm going to be saying more about that in a couple of minutes.

Another interesting topic over the past year has been the h term outcome of people who become delirious. So we've all sort of grown up with the teaching that delirium is an acute event. It's caused by some underlying medical problem. We treat the underlying medical problem, i.e. the urosepsis, the pneumonia, the hip fracture-- whatever it is-- and the delirium goes away. That's kind of the classic teaching on delirium is that it gets better.

Well, unfortunately, it doesn't always get better. And so I'm going to spend a couple minutes looking at that. This was a very interesting study from *JAMA Psychiatry.* There is a brain autopsy bank in Europe where they've got 1,000 brains-- this IS people who have already passed away, who've already been autopsied-- and they've done a series of substudies of this brain bank over the years. This particular study was they did a look-back at six years prior to the death. So these people are all dead. But they did a six-year look back study of who had an episode of delirium in the six years before they died.

This study has been going on for several decades now. So they were diagnosing delirium by an older version of the DSM-- the III-R. And they weren't using MoCAs, as they were using MMSEs, because the MoCA had not yet been invented when they started collecting all these brains.

So they looked at dementia pathology, which they defined as neurofibrillary tangles, plaques, Lewy bodies, vascular lesions. And what they found was that people that had a delirium episode did worse than people who didn't have a delirium episode in terms of the rate of progression. So this is divided by people with most dementia pathology at autopsy and less. But for both types of patients, if there was a delirium episode, the rate of getting worse in the six years prior to death was significantly worse than if they didn't have a delirium episode.

I mentioned that severity is becoming increasingly important in looking at delirium outcome. This was a study looking at about 600 patients who were graded into full delirium or partial delirium, which would call subsyndromal delirium. Subsyndromal means they meet some but not all of the features of becoming delirious. And what these folks showed was that if you had no delirium, subsyndromal delirium, and full delirium. And it's pretty clear that these graphs diverge, and people with the full syndrome of delirium do worse in the subsequent three years after an episode of delirium.

So getting back to pathophysiology, this was a nice graphic that was just published a couple of months ago. This is from the group that is headed by Dr. Sharon Inouye, who is sort of the leader in thinking about delirium. Fong was one of her fellows and is now one of her collaborators. So they sort of made this up, that vulnerable brains, versus normal resilient brains, that are subjected to enough of a stress are going to have a period where they don't get better-- persistent delirium. We know, clinically, this happens. We know that about a third of delirious patients will persist for many months, and some of those people with persistent delirium are going to shade right on into permanent cognitive impairment after an episode of delirium.

So what I'm showing you doesn't tell you anything that you don't already know. You've all seen this at the bedside, that people sometimes don't get better. But they're trying to understand, why is that-- what's going on in these brains that don't get better?

They're looking at biomarkers to try and understand this. These are some of the biomarkers that are being studied right this minute. Again, this is not anything that we're going to be able to use right now, but it's really kind of interesting to think about what's causing delirium that doesn't get better.

Turning to treatment of delirium, these three items have all been proposed as ways to prevent or treat an episode of delirium. And we have new information on all three of these things from within the past year. So the first is antipsychotics. Our friends at the Cochrane collaborative did a systematic review of antipsychotics for prevention or treatment of delirium. And the bottom line is, they don't work.

They don't do anything useful, except that if the patient is a harm to themselves or to the people trying to take care of them, it's OK to use antipsychotics. Antipsychotics essentially convert a hyperactive to a hypoactive delirium, but they don't make the person not be delirious. So we try not to use the antipsychotics. But if we must because otherwise they're pulling out their NG tube, or they're pulling at their central line, or they're punching everybody who comes near them, you have to do that. But we shouldn't delude ourselves that we're actually treating delirium with antipsychotics.

So this is the forest plot, looking at severity of delirium with an antipsychotic versus a placebo. And you can see, it necrosis the zero line, wherever my pointer is. Here we go. So there's no there's no difference.

This is some time to resolution, antipsychotic versus placebo. No difference. This is using antipsychotics prophylactically-- before the patient is delirious, when they come into the hospital. Giving them something like haloperidol when they come in the hospital to prevent delirium, does that work? And although there have been some studies showing that it does work, the systematic review of all the studies is that it does not work.

So moving from antipsychotics to cholinesterase inhibitors, such as donepezil or rivastigmine, it has been hypothesized, in some studies, that prophylactic donepezil, for instance, which is Aricept, might prevent delirium. And the data is that it does not work. Melatonin has been proposed as something that might prevent delirium. And again, it doesn't do anything better than placebo. Another study looking at melatonin published recently in the *American Journal of Medicine*-- this was a small study, 69 patients, melatonin versus placebo. And I thought this was interesting, not only because it didn't do anything for preventing delirium, but it also didn't do anything to promote sleep either.

We currently are using melatonin, all the time, every day, in our hospitalized patients, in our outpatients. We're trying to give a patients melatonin, because we think that it's a nice, safe way to help them sleep. But it looks like it's about the same as giving your patient a placebo. Which is to say, it works about a third of the time, just like placebo does, but not any better than that.

OK, changing the subject to delirium in the intensive care unit. There have been a number of studies published in the last 12 months looking at ICU delirium. And what I'm showing you here is a very well-publicized study. This was a review of ICU delirium published in the *New England Journal of Medicine* in 2014. I'm going to show you what we've learned since then.

At that time, the controversy was over what's called sedation-related delirium. Which means if the patient is on propofol or lorazepam or dexmedetomidine and they're gorked, is that delirium? Well, you made them that way. And in order to say that they are delirious, you have to give them sort of a drug holiday. You have to stop the drug, and let them lighten up, and then assess them. So that's been clarified since this 2014 report.

There was a question back then whether dexmedetomidine, which is Precedex, is safer than propofol or other sedating medicines. If somebody is on the ventilator, and they're bucking the ventilator, and they have to be sedated, and you have to give them something, is dexmedetomidine less deliriogenic than other drugs? There's increasing evidence that it is, but the jury's still out on that. There was some question, do statin drugs prevent patients from becoming delirious in the ICU? There were a number of smaller studies suggesting, yes, that statins prevent delirium. But more recent studies, unfortunately, are no.

So the Society of Critical Care Medicine, at about that time, came out with this bundle-- the ABCDEF bundle-- which is currently in use at all of the UPMC hospitals. And it's probably in use and every hospital. It makes perfectly good sense. This is not evidence-based, this is consensus-based. They're talking about controlling pain, getting people off the ventilators, early mobilization, preventing delirium. I think everybody would agree that this makes sense to do.

Within the past year, there was actually a study of, does it in fact make sense? Does doing this bundle lead to better outcomes? And this was a huge study-- a national study, 68 sites, 15,000 patients-- and they found that, in fact, following the bundle does lead to better outcomes. And they were able to measure adherence at all of these different intensive care units. And they found a dose response curve-- the more adherence to the bundle guidelines, the better the patients did. So that was very reassuring to see that.

Also, in the past year, the same group came out with another set of consensus-based guidelines that go by the acronym of PADIS, which is Pain, Agitation, Delirium, Immobility, and Sleep. They came out with a laundry list of recommendations. What I've shown you here are the ones that specifically pertain to delirium. And again, this sort of has great face validity, that we can identify risk factors, that we should screen for it, and that trying to prevent it doesn't work. Don't use an antipsychotic-- high face validity for these things.

They recommend that we use dex if we have to sedate somebody on a ventilator. Bright light therapy doesn't work. Multicomponent, nonpharmacological intervention focused on reducing modifiable risk factors, et cetera-- so this has good face validity. But again, it's a consensus-based document.

So meanwhile, the killjoys that the Cochrane collaborative, where they believe in systematic reviews rather than consensus-based guidelines, also looked at the data. And they felt that there was insufficient evidence to support what I just showed you on the previous slide. So they're not saying that the PADIS guidelines are wrong, they're just saying that there's insufficient evidence to prove that they're right. So that doesn't mean we shouldn't do these things, just we should be aware that the evidence isn't quite there yet. And again, all these references are in your handouts.

So this, I thought, was amusing-- that is a robot cat. And this a patient in ICU. The idea is that you can calm an agitated patient by giving them a robot cat to play with. The study was really small. It was of note, but the science was zero in this study. I was amazed that it got published.

[LAUGHTER]

But it's really interesting to look at this. It seemed to me, this is a great vehicle for transmitting bacteria between patients.

[LAUGHTER]

So changing the subject to delirium in the emergency room-- there was a retrospective study of an administrative database looking at literally millions of patients who came to the emergency room in this country for 2012-2013. Of those, they identified 26,000 cases of delirium. And we're talking of everybody who came to the emergency room in this two-year period. The weakness of this study-- the big weakness-- of course, is that this is administrative data. It's based on ICD-9 diagnoses that somebody wrote down on a piece of paper, it's not based on was the patient really delirious.

We know from other studies of delirium that go by administrative databases that they probably miss at least 90%, if not 98%, of all the cases of delirium. So these were, presumably, the very worst, hyperactive, running around the emergency room naked-- this is probably those cases. But they found that the 30-day mortality was five times greater than controls who did not have delirium. The mortality rate at 30 days was 12%, which is comparable to the mortality from an acute MI.

So this is important. And in my opinion, if somebody in the emergency room has delirium, that person should be hospitalized. Because it's a highly morbid and highly mortal condition.

There are guidelines that have been put out for treating delirium in the ER. Again, these are consensus-based guidelines from an academic society. This is ACEP-- American College of Emergency Physicians. And you can see what ADEPT stands for-- again, very high face validity and pretty similar to the ICU guidelines.

So moving on-- now, I want to talk about postoperative delirium. And before I talk about postoperative delirium, I want to talk about Postoperative Cognitive Dysfunction or POCD. So you see the first report of something happening postoperatively was way back in 1887-- insanity following the use of anesthetics and operations. So since then, there's sort of two bad things that happened to brains after surgery. One is delirium, and the other is this vague entity called postoperative cognitive dysfunction.

So POCD is not in the DSM. Delirium, as I showed you at the beginning, is. POCD is not in the DSM. It's not an official diagnosis. But here's what the working diagnosis is-- a subtle cognitive decline following surgery and general anesthesia, diagnosed by pre and post-neuropsychiatric testing, that does not meet criteria for delirium or dementia.

So in order to diagnose your patient with proceeds you have to know their baseline. Without knowing baseline, one can't say. And the problem with POCD is that it's a real thing-- you've all seen it. And it can persist in elderly people for a year or more. And if something persists for more than a year, we might think they're moving on to a mild cognitive impairment or early dementia.

The first good study of POCD came from Johns Hopkins in 2008. So that's a little older, but worth reminding everybody, this was a study of 1,000 people who at baseline were cognitively normal. They did have baseline psychometric testing. And then, post-op, they had repeated psychometric testing which continued for several-- I think they did it at maybe a week, and then three months, and then 12 months.

And you can see that at three months, among people over the age of 70, 13% we're still not back to their premorbid baseline. So that's substantial. And at a year, a significant number were not only still impaired, but dead-- increased death rate, even with this vaguely defined entity.

So there is a good study that is underway right this minute. It's called the INTUIT study. It's happening at Duke University. They are, right now, still enrolling patients. I'm not sure if they've completed their enrollment or not.

But they've managed to enroll patients who are agreeing to pre and post-blood tests and lumbar punctures. They're looking at blood and CSF biomarkers of various substances, which I've shown here. And they're doing functional MRIs, psychometric testing, physical function testing of 200 patients to see what happens postoperatively. So this is hopefully going to tell us a lot more about what is POCD. But we're going to have to wait a couple years to hear from them.

So turning from POCD to our friend delirium, this was an interesting study from the province of Ontario in Canada. They looked at post-op delirium in hip fracture patients versus how many minutes was the patient in the OR. So that's what this is. And you can see, pretty much, that the longer the surgery in minutes, the greater the risk of the patient becoming delirious. Pretty interesting.

This was a study a couple of years ago of delirium in patients undergoing coronary bypass grafting. And this was people who did and didn't get delirious. The group that got delirious dropped their MMSEs, and they stayed down, even at six month follow-up.

So that study led to this study. This is called the Successful Aging after Elective Surgery or SAGES study. This is, again, the Sharon Inouye at the Beth Israel Deaconess hospital in Boston. They enrolled patients not only at the BI but also across the street at the Brigham Hospital-- 566 patients over the age of 70. And they've put out a whole series of publications based on this one study, and these have been very well done studies.

So what they've shown is that of these people who were not delirious or demented at baseline, about a quarter of them develop postoperative delirium. And this was carefully done. This was baseline psychometric testing and an every day careful assessment by trained researchers, postoperatively. If they had any kind of baseline cognitive dysfunction, they were more likely to be delirious afterwards, which we know from previous studies. The degree of baseline impairment correlated with the risk of becoming delirious postoperatively. And, as I said a couple minutes ago, both the severity and the duration of delirium are associated with worse outcomes.

Delirious patients spent more time in the hospital, more likely to go to a SNF, more likely to be readmitted to the acute hospital with some sort of a problem. They looked at delirium compared to other post-op complications, such as MI, sepsis, et cetera, and found that delirium was actually more predictive of longer hospital stay than things like having a post-op MI. All patients got worse after surgery in terms of function, but the delirium cohort stayed worse for at least 18 months of follow-up compared to the nondelirious cohort.

They measured plasma CRP, and found that they were higher in delirious patients. So they hypothesized that this is a marker of neuroinflammation. And we're going to find out much more about that in the next couple of years-- about CRP levels and delirium.

This was, again, the same study-- the SAGES study-- published within the past year. Delirium severity and long-term cognitive decline-- so the bottom line, this line-- these are the people that were most severely delirious. And you can see, over the three years of this follow-up after they had surgery, they did worse than people that didn't have delirium. This was another sub study of SAGES-- Cavallari is a neuroradiologist at the Brigham, and she did MRIs prior to surgery, showing that people that had MRI changes were more likely to get delirious. And she also did postoperative MRIs, and found that up to a year later there were MRI changes in people that got delirious, compared to people that didn't get delirious.

So these delirious patients' brains had changed as a result of their delirious episode. So it's not just that somebody's CRP went up or some biomarker went up, but you can see MRI changes in the brain of somebody who had a severe case of delirium. So what do we do with that information? I don't know. More to come-- but this is certainly new information that you can actually see abnormalities in a delirious brain on MRI.

So what are we supposed to do with delirium? Obviously, prevent it. These are some guidelines that came out of the anesthesia literature. So this is not the literature that we in this room tend to read, but there's two sets of guidelines from anesthesia. I've combined them here into one slide and divided into pre-op, intra-op, and post-op.

The intra-op are things that are not under our control. This is things like should patients be monitored with EEGs, during surgery, while they're in the OR, to have them be as light as possible. Would giving enough anesthesia but less than they might otherwise get, would that result in less delirium? The jury is out on that. There are some studies that say, yes, EEG monitoring produces less delirium. There's other studies that say it doesn't make any difference. So we'll have to wait and see, but this is what the anesthesiologists are talking about right now.

So turning from diagnosis and treatment to prevention-- that's where we have an opportunity. Everybody in this room has an opportunity to prevent delirium, right now, today. The best way to prevent delirium is with a multicomponent, targeted intervention. And the best of those-- probably, everybody knows this-- is called the Hospital Elder Life Program. So I want to take a minute and mention the Hospital Elder Life Program. And there's been some new publications on HELP within the past year, also.

So as I review, the idea is to identify elderly in-patients over the age of 70 who have risk factors. And we already know with those risk factors are-- baseline functional impairment, baseline cognitive impairment, vision and hearing impairment, and so forth. Train a cadre of volunteer workers-- mostly these are college students-- pre health care professional students, like premed students, nursing students-- to go to the patient bedsides and do these simple interventions to hopefully prevent them from becoming delirious. It's been shown that this works and that the HELP interventions do prevent delirium.

So this was, again, a Cochrane collaborative review, published within the past year, looking at the Hospital Elder Life Program and some other programs similar to it. And what they found was that, in fact, it works, and it reduced the incidence of delirium by 30%. Pretty good.

These are the health interventions. I'm not going to go through them-- but again, in your handout. These are the things that we have the volunteers target at the bedside to try and help the patient do better. This is actually an actual volunteer and an actual patient from Shadyside Hospital. Both of them did give permission to have their pictures shown. And this person is helping the patient ambulate. This particular volunteer was a college student who did subsequently go on to become a physical therapist. And she currently works at UPMC.

So this is our data from Shadyside. We've been doing help now since 2002 at Shadyside side. Our baseline delirium rate, in the upper-left hand corner, 41% before we did anything on one general medicine 40-bed nursing unit. It took us a little while to get our act together. But after we did, we were able to reduce the total delirium rate to only about half of what it had been before.

This orange line at the bottom is incident delirium. There's two kinds of delirium, as you all know. Prevalent delirium means the patient came in that way. Incident delirium means they were not delirious when they came in, but they became delirious on our watch. We can't prevent prevalent delirium, but we, presumably, can prevent some cases of incident delirium.

So for the kinds of patients we looked at, the incident delirium expected rate for these general medicine, frail elderly patients would be about 20%. And you see, it's 3% or 4%. And we've held the gains for all these years. This data is through this past December-- it's through four months ago.

This is the number of patients that we treat at Shadyside, which is over 7,000 patients a year. We do have the largest health program in the world right here at Shadyside. We've had lots of visitors come from all over the world to Pittsburgh to look at what we do, which is gratifying for us. And this was a recent study that we published, looking at the readmission rate for patients who were in HELP versus patients who were not in HELP. And we did reduce the readmission rate, and that equaled about 100 readmissions per year-- 100 patients who didn't get readmitted because they were in HELP.

This study is not Shadyside side data. This was a systematic review, again, from Sharon Inouye's group, looking at all of the HELP sites around the world that have published their data. And what they found was that HELP, in general, reduces delirium, reduces falls, costs of care, length stay, transfers to long-term care facilities. So certainly the data exists-- the data is there-- that this program works, and we should all be doing it at our hospitals.

So are we doing good it at our hospitals? In Pittsburgh, these are the only three hospitals I know of where we are doing it. A number of hospitals have thought about it or are considering it. But as far as I know, nobody else has actually implemented it. If any if anybody at a Pittsburgh-area hospital is interested, we at Shadyside side are available to help. We offer help freely to anybody who would like to get a program started.

And these are some interesting delirium references for you. These are the online resources. Again, I would call your attention to hospitalelderlifeprogram.org. They really have everything, including this wonderful bibliography.

And I'm going to end with a picture of an actual patient of mine who grew this giant zucchini in her backyard.

[LAUGHTER]

And if she can do that, then we can work on delirium.

[LAUGHTER]

So I will quit there. Thank you for your attention.

[APPLAUSE]