Dr. McPherson: Hello, this is Dr. Lynn McPherson and welcome to Palliative Care Chat, the podcast brought to you by the online Master of Science and Graduate Certificate Program at the University of Maryland. I am so excited about our guest today, I can barely contain myself. We have Dr. Jason Webb, who is an Assistant Professor of Medicine, Psychiatry, and Behavioral Medicine at Duke University School of Medicine. He completed his internship and residency in internal medicine and psychiatry at Duke University School of Medicine, and followed up with a fellowship in hospice and palliative medicine.

Dr. McPherson: So, this man is a triple threat. He is boarded in internal medicine, hospice and palliative care, psychiatry neurology, and psychiatry. So, wow, I know when I was a pharmacy student I thought, "I don't know what I'm gonna do when I grow up, but it's not gonna have anything to do with psych, because it's just too complicated," and look at you! Dr. Webb, welcome! We're delighted to have you.

Dr. Webb: Thank you very much. It's always humbling to hear the triple threat.

Dr. McPherson: You are a triple threat, you're a scary dude here. You're so smart, good grief. So you are probably the smartest person in the world about psych issues and end of life. So, I have so many questions. Can we jump in?

Dr. Webb: Yeah, please.

Dr. McPherson: Okay, so the one thing that makes me crazy is why do so many clinicians use quetiapine, Seroquel, for sleep? We see this all the time. What are your thoughts on that?

Dr. Webb: Yeah, to be honest, it's really frustrating because... you know, I sort of joke around with my house staff that I think some of the time that people use it just because Seroquel, for some reason, can be easier to sell than other things. But I think, really, people figured out that this is a sedating medication because it's essentially a really inexpensive form of Benadryl. It's a strong antihistamine.

Dr. Webb: And I think people don't know any better than to pick something to use that, particularly in this day and age with the opiate concerns, is that people are trying to avoid, probably rightly so, benzodiazepines, the non-benzodiazepines, diazepines like Ambien due to the risk for respiratory issues. So somehow or another, quetiapine or Seroquel seems like a safer alternative despite the toxicities and side effects the medication can have.

Dr. McPherson: So what do you think about that? Do you think Seroquel is safer than, well benzos with a strong anticholinergic effect concern me, but do you think it's safer than the benzos and the non-benzo Z drugs? What are your thoughts?

Dr. Webb: Well, I think it entirely depends on the patient population that you're taking care of. I would argue that there are lots of good nonpharmacologic ways of managing insomnia, cognitive behavioral therapy for example is highly underutilized, so for a lot of people there's not great access to it. I think there are other antihistamines that can simply be used. For example, like doxepin, at very low dosages was recently FDA approved in a different formulation called Silenor, which is super duper expensive and there's no reason to not just use like a 10 milligram dose.

Dr. Webb: But I think particularly for patients who have difficulty with sleep initiation, which is essentially falling asleep, folks have found quetiapine can be useful for some patients, however, if you have patients with dementia, if you have patients with other neurocognitive impairments, if you have folks who are at risks for falls or the elderly, particularly with the alpha-adrenergic effect of quetiapine which is highly potent at the alpha receptor, and it's not a good choice for a lot of folks. And particularly in the long run, there are other risks developing and, for a person that doesn't have Parkinson's some Parkinson’s, 'cause it is a dopamine antagonist so it has a low afinity.

Dr. McPherson: Mm-hmm (affirmative).

Dr. Webb: And the victims all report a metabolic side affect with this, with the agent. So, I think non-pharmacologic intervention, melatonin, CBT, or welthian would be an alternative to using this. And I think a lot of people just they see it used in the hospital and for some reason think it's a good, safer alternative.

Dr. McPherson: Mm-hmm (affirmative). So you mentioned psychoses. Should Seroquel be used for psychoses? And I'm particularly interested in ... Everybody seems to grab Seroquel for patients who have delirium with Parkinson's disease. So when should we use it in general for psychoses and what do you think about Parkinson's disease?

Dr. Webb: Yeah, so I think when we're talking about psychosis we have to make that we're kind of grouping things into the appropriate psychotic symptoms. So for a patient with a true, true psychotic disorder, like bipolar mania, schizophrenia, schizo-affective disorder, this can be an effective tool for managing psychotic symptoms.

Dr. Webb: Now, this is typically way above the dose that general internists or palliative care doctors would be used to. We're talking dosages of quetiapine in a four to six hundred milligram range.

Dr. McPherson: Wow.

Dr. Webb: Where you're actually getting some Dq antagonism, in addition to the sort of serotonergic effect of the drug.

Dr. McPherson: Mm-hmm (affirmative).

Dr. Webb: So, for patients with true psychotic disorder, we're using real, true psychotic dosing, antipsychotic dosing of quetiapine. Which is something that, particularly you'll never see in an ICU, you'll never see in a medical setting where people are using 12.5 milligrams, 25, 50, maybe 100 milligrams.

Dr. McPherson: Mm-hmm (affirmative).

Dr. Webb: And really, at that low dose you're just getting strong antihistamines, you're getting a sedative effect of the drug. I think in patients with Parkinson's disease psychosis, for a long time, we ... and there are guidelines published in American Journal of Psychiatry, recommendations for using quetiapine for Parkinson's psychosis. Primarily for the fact that this is just kind of a strong antihistamine. It was sedating.

Dr. Webb: But I think what we didn't realize was that a lot of the antipsychotic benefit was really coming from targeting serotonin 5HTQA, 5HT2C receptors, with the drug. And that ... So people would use it in that sort of off label formulation. But reality is that actually for Parkinson's psychosis, if you look at the meta analyses and some of the RCTs, actually clozapine for the long time actually have the best data. There was randomized controlled file data showing that Clozaril could be used for Parkinson's psychosis. But nobody uses that stuff in the United States because of the blood dyscrasias and the risks associated with it, and also just the monitoring.

Dr. Webb: So if you're in the hospital doing a palliative care consult for a patient that's Parkinson's psychosis, nobody's gonna pull out Clozaril or use that unless you're trained as a psychiatrist and have approval to use it.

Dr. McPherson: Mm-hmm (affirmative).

Dr. Webb: So, it wasn't until Inovanseran came along, in the last few years, that there's really actually been a non-dopamine blocking agent that's been potentially useful for this. And it has a much more novel mechanism of action than any of the prior drugs.

Dr. Webb: So, long answer, way to answer your question. Yes, you could use quetiapine primarily because it's more of an antihistamine, it has 5HTQA, QC antagonism. But there's probably a better agent now which is Inovanseran, which has no DQ antagonism, and only selectively blocks those serotonin receptors, which we think probably is part of the driver enforced in Parkinson's disease psychosis.

Dr. McPherson: It's interesting, the mechanism of Inovanseran is inverse agonist and antagonist. Initially they called that a contragonist. What are your thoughts on this crazy mechanism of action?

Dr. Webb: Well, you know again, quite novel that they discovered this that the ... Basically this is a drug where they're blocking 5HTQA receptors and then also agonizing inverse agonism of those receptors. And that's the most potent mechanism for the drug. There's less potency at the 5HTQC receptor, and it has again a similar antagonist inverse agonist action.

Dr. Webb: And this is really the first example of a drug that has, quote unquote, antipsychotic action that didn't block DQ receptors. And there was some initial kind of controversy around this agent. And as they continued to follow it's use, it's seemingly effective with probably better safety in patients, particularly if you've got other patients [inaudible 00:08:26] with like Lewy Body Dementia, patients with Alzheimer's type disease that have some Parkinsonian features, where you're worried that any sort of blockade at the D2 receptor may worsen that symptomatology.

Dr. Webb: But this has a really interesting mechanism of action. And so the idea that you could help with psychosis primarily only by blocking serotonin receptors, and then also sort of reversely agonizing, I think is where this drug has some really interesting utility.

Dr. Webb: And I'll say in the few times we've used it, it's actually been really relatively impressive. I don't have a huge case log to talk about it, but I've seen it work effectively, and in that very specific patient population of Parkinson's disease.

Dr. McPherson: Mm-hmm (affirmative). Just one word about Clozaril, I don't think a hospice or palliative care provider, particularly a hospice person, would start Clozaril for Parkinson's disease psychoses, because you're right about the monitoring. But I do want to point out that if someone's been getting Clozaril consistently and being followed by mental health care practitioner, if the patient is admitted to hospice, potentially for an unrelated reason, if you go to the Clozaril REMs page there is a form that the physician can sign to do away with the white blood cell count monitoring for the next six months. It's Clozaril REMs dot com. So I thought that was interesting.

Dr. McPherson: So from a pharmical economic perspective though, since I'm the hospice drug girl, when you're looking at Parkinson's disease psychoses and you had to prioritize Seroquel, Clozaril, or Pivovantrin, which is thousands of dollars a month. How would you put this in the pecking order?

Dr. Webb: Yeah and I think that's really important and I think that's one of the challenges that we run into. And I think one, to your point about, if you have a patient that comes off hospice, but even for example if you've been started on Clozaril for psychosis and they get admitted to you hospice, please don't stop the medication. There are ways to make sure that you can get it.

Dr. Webb: And then I think one of the realities is that we have to make a choice for our patients not to incur worsening financial toxicity as we approach the end of

patients' lives. At the same time, making sure that we're picking medicines that can be effective. So I think in that case, I think for a lot of patients, we tend to typically use quetiapine, because it's ... Again, there's not as much hoops to jump through. There are some facilities where people are more familiar with it's use. So the data that each that alternative, is probably not in the future. Hopefully therapy if taken an issue over time, and hopefully as the practice go down we could use more Pivotarin in the hospice setting.

Dr. Webb: But I think now if you have a patient really that is having symptomatic psychosis that's effecting their quality of life, that quetiapine would be a reasonable option to try.

Dr. McPherson: Okay.

Dr. Webb: And again, if you want to be a little bit more evidence based, you could try Clozaril and you could get the dispensation to be able to do that. And I think some concern because of the cost would be kind of third on the list in that setting.

Dr. McPherson: Mm-hmm (affirmative). What kind of doses of Seroquel are you using for psychoses in that situation? Would you start at 25 TID? How would you dose that?

Dr. Webb: Yeah, so I think with any of these medications it's always start low, go slow. And so, it's typically, and I think depending on other Parkinson's type symptoms, and what I teach our fellows, is that one of the big things that you don't want to do clinically if you have somebody who's still at home, who's potentially still a little bit ambulatory, is to cause them to have a fall. Specifically start at 12.5 milligrams BID PRN, and then sort of treat to effect. And if that just doesn't work then slowly escalate the dose to 25 milligrams maybe QH, and then just sort of assess what the daily dosage is to use. And talk to the family about monitoring for any symptoms of sort of orthostasis, and particularly as you get the sedating that's after this medication.

Dr. McPherson: Mm-hmm (affirmative).

Dr. Webb: And a lot of it is also just the conversation with caregivers about what the goal is of the therapy-

Dr. McPherson: Sure.

Dr. Webb: Is it ... The treatment is that we're trying to target symptoms that are causing a detriment of quality of life. And so, really the goal isn't to sedate the patient, it's to try to see if we can decrease the psychotic symptoms or agitation to a point that they can have a good quality of life, participate in the things that they enjoy doing, for as long as we can.

Dr. McPherson: Mm-hmm (affirmative). I just know it's a real struggle in hospice when these medications come on the market that ... Even some of the older drugs like the cholinesterase inhibitors and memantine, they're still fairly expensive. And you wonder, how much of an effect are you really getting? So between those medications and now this Pimovantarin, and Nuedexta's the one that we're hear about with suitable [inaudible 00:13:04]. These are really expensive medications. And it's really difficult in hospice to have that conversation with the patient and the family and the caregivers. Often, more often than not, we see a point of diminishing return and that's a difficult conversation.

Dr. McPherson: I'd like to go back to one other thing you mentioned earlier. You briefly mentioned something about reversal of the sleep wake cycle, which I've kind of always associated as an early sign of impending delirium. What are your thoughts on that and how would you treat that? The family gets exhausted with the patient basically awake all night long.

Dr. Webb: Yeah. No, I think that's one of the biggest challenges that we hear from families is when that sleep/wake reversal happens. And it's often times, to me, also a sign when you start to see behavioral changes that the brain is not functioning well. There's more acute unchronic brain failure happening to this patient.

Dr. Webb: And so often times the non pharmacologic interventions of trying to engage the patient as much during the day time, a well lit home, well lit hospital room to try to keep people awake during the day. There's some suggestions that using melatonin, and particularly the mistake that some people make and if you talk to some of the sleep experts, is that they'll try to get melatonin once ... when it's dark already to try to get people to go to sleep. And really what the brain normally does is start to secrete melatonin at dusk, with a peek onset of melatonin in the brain at the time of sleep initiation, to sort of help with sleep maintenance.

Dr. Webb: So I typically recommend that they start to give the melatonin actually a couple of hours before you would anticipate bedtime to try to get a peek concentration to really try to help with the sleep/wake cycle. For some folks it's some classic music and a little bit of maybe a glass of warm milk to sort of help with that cycling.

Dr. Webb: I think there are other options to maintain cycles that wouldn't be ... Getting back to the question of using quetiapine for sleep, for some patients Trazodone can have some effectiveness for helping kind of maintaining sleep/wake cycle. Again there is some orthostasis there as well that you have to sort of monitor. And for some of our patients where there is a bit more of a need for ongoing sleep maintenance, again I mentioned that things like low doses of doxipans can be helpful in that setting as well.

Dr. McPherson: Okay.

Dr. Webb: So I typically use that for healthier patients.

Dr. McPherson: Mm-hmm (affirmative). Would you ever consider using methyphenidate during the day to perk the patient up so hopefully they would be a little sleepier later?

Dr. Webb: No, to be honest, I've actually not done that for patients particularly with sleep/wake reversal. Again it's sort of, yeah we're treating one thing and then if they get agitated at night, trying to avoid some of that polypharmacy-

Dr. McPherson: Sure.

Dr. Webb: It definitely is kind of more the tactic that I kind of recommend.

Dr. McPherson: Okay. Well let's switch gears for a second. You and I did a podcast oh, about a year or so ago when that big study came out of Australia looking at haloperidol and Risperdal versus placebo for patients who were receiving palliative care in an inpatient Australian unit. And they show that the active drugs actually led to death sooner than the placebo, so it caused quite a stir. So we had a lovely conversation about that.

Dr. McPherson: And I just the other day I got an email from a colleague saying, "Well this is the final nail in the coffin for Haldol, referring to this paper published in October of this year in New England Journal of Medicine, titled, "Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness." So what are your thoughts ... Are you familiar with that study?

Dr. Webb: I am, yes.

Dr. McPherson: What are your thoughts on that?

Dr. Webb: Yeah, so really interesting study, also, yeah kind of frustrating in trying to kind of purpose together in the grand scheme of how to manage delirium, and particularly the role of antidopaminergic medication. So, briefly, the take home was that this was a study in the intensive care unit, primarily with patients with shock from sepsis, also with respiratory failure. Where they looked at comparing Haldol versus placebo or ziprasidone, which is a second generation agent, versus placebo. And their primary outcome was to look at the number of days alive free from delirium over a 14 day course of the treatment.

Dr. Webb: So they were using this kind of as a treatment to try to decrease delirium duration, and kind of a pre-treatment once the onset turns on. And then also looked at a lot of secondary outcomes, in particular mortality, toxicities associated with these agents.

Dr. Webb: And the big take home was that there were really no ... Their primary outcomes didn't show any improvements in the number of days free from delirium in the 14 days of the study. And there were no significant secondary outcomes,

including toxicities which is really important because the doses of Haloperidol and ziprasidone that they used in this trial, in particular Haloperidol, were really high. Primarily on average I think 10 milligrams a day, up to 20 milligrams of haloperidol.

Dr. McPherson: Wow.

Dr. Webb: And to be honest ... Yeah! And to be honest, the majority of the patients in the study, if you look at their ... table 2 where they give the demographics up front, was that the majority of the patients actually have hypoactive delirium. And they appropriately used the best validated way of assessing delirium, which is they used the Cam ICU. And they designated if it was hypoactive versus hyperactive using their RASS score, which is Richmond Agitation Sedation Scale. And so if you had a positive Cam and then a RASS less than zero, they had hypoactive delirium, which really meant that they were sort of sedated or sleepy and less responsive.

Dr. Webb: What I would say the take home was that if you ... This trial looked at patients that were sick but shocked with respiratory failure who were primarily hypoactively delirious, who were treated with either a first generation agent Haloperidol or ziprasidone. And my kind of big takeaways from this is that these agents don't decrease the duration of delirium in the ICU when they're used at pretty high dosages.

Dr. Webb: So one just sort of clinical practice takeaways, I never used ziprasidone. Honestly, in four years of practicing as a palliative care provider, here at Duke, and primarily just based on the QPC prolongation risk at that age, and ... I've never prescribed it. Like literally have never prescribed the drug. And I don't think a lot of people, particularly in our practice here, don't use the drug as commonly.

Dr. Webb: In addition I would say that most of us don't prescribe antidopaminergic agents for patients who just have hypoactive delirium. I mean I think most of the time where we're using these are for patients with agitated, psychotic delirium-

Dr. McPherson: Mm-hmm (affirmative).

Dr. Webb: And particularly at the very end of life when patients are symptomatic. And so I think for us in the palliative care population, when we're seeing patients in the Intensive Care Unit, I don't think that we would use 10 milligrams of Haloperidol to manage psychoactive delirium.

Dr. McPherson: Mm-hmm (affirmative), that's a big gun, huh?

Dr. Webb: It is. So think that, really what that does tell us though is I think for ... For outcomes in the ICU, particularly when patients have end organ dysfunction, which we think delirium in an anti-secure unit when someone's critically ill is a

sign of end organ dysfunction. Is that the trial does tell us that using these agents aren't going to decrease the duration of delirium, and what it also does show is that it didn't necessarily hurt anybody.

Dr. Webb: So I think what they do ... kind of make that comment in their critique in the article, is that, while you can't apply this to other agents ... So again, as we had talked about the prior trial, what we don't know is what olanzapine or even Clotiapine or something a bit more sedating. Ziprasidone is probably moderately antihistaminergic. But would something that's quite a bit more antihistaminergic potentially help more for somebody with an agitated, hyperactive delirium?

Dr. Webb: And this trail doesn't answer that question in the intensive care unit. And so really I think, also it's a little harder to extrapolate this to a patient in the last hours or days of life in the intensive care unit who also has the hyperactive irreversible delirium. These are patients where when they're in the ICU with shock, with respiratory failure, if this is a reversible problem... again I don't think that we would often times use these agents first line and we would try to reverse medical reasons why the patient's delirious, try other nonpharmacologic interventions.

Dr. McPherson: Mm-hmm (affirmative).

Dr. Webb: So I think it gives us a little bit more pause about when we do use those, particularly in the ICU. But I think it leaves more questions than answers, particularly for patients who are symptomatic, agitated, psychotic at the end of life. And so ... What's great to see is that there's these studies happening. They give us more information about how to better choose medications, choose dosages, but it often times for me leaves more questions than answers.

Dr. McPherson: You know, when I was reading that study, it dawned on me, I was like, "Oh my gosh." I don't think we routinely screen for hypoactive delirium. I've always kind of referred to these folks as the quietly confused, and it always seems like they've got a lot going on. Are we dropping the ball? Should we be doing a better job screening for hypoactive delirium in hospice care or in palliative care a little earlier, before hospice? And should we be treating it more aggressively?

Dr. Webb: Yeah, so well I think based on the fact that we know that hypoactive delirium is a strong indicator of mortality, it's a stronger indicator of mortality if you look at the evidence compared to hyperactive delirium-

Dr. McPherson: Right.

Dr. Webb: But we tend to mix them, as you said it's sort of a quietly confused patient. And particularly in medical settings when somebody is quietly confused, the family will often times notice that first. And part of what I teach our trainees is that if the family member says, "Something's not right with my mom, she's confused."

Dr. McPherson: Mm-hmm (affirmative).

Dr. Webb: And that's not an agitated patient. That requires some deeper investigation of doing some assessments like using the Cam, using the RASS type of assessments for delirium. And then trying to determine if there are any reversible things happening. Like is this patient ... Is there a way to get the patient better hydrated? Do you think they just need their glasses and their hearing aids and they need to be up and ambulated as possible. So are there interventions that we can do to try to help restore or reverse that acute cognitive impairment.

Dr. Webb: And so I think we do probably need to do a much better job of that, and I think a lot of health systems are trying to implement ways of better assessing and screening for patients where we could try to make some better interventions up front. I think we run into the challenge, and pops up in palliative care, that a lot of our patients develop delirium that's irreversible, that's part of the transition towards the very end of their life.

Dr. Webb: And whether, or not, again I think there's a lot of controversy, of whether, or not we should be pharmacologically treating hypoactive delirium. I would argue that we-

Dr. McPherson: That was my next question.

Dr. Webb: Yeah, I think ... I don't know that we should. I think, again, part of it is trying to assess what are the end ... For these patients part of what you're trying to assess is if you're seeing somebody who's hypoactive delirious and if that means again, they have an impairment in attention and concentration.

Dr. McPherson: Mm-hmm (affirmative).

Dr. Webb: They can't attend to tasks, they can't pay attention, they can't follow along, they can't appropriately answer some cognitive questions with what they're oriented. Yet those patients, unless they're symptomatic, I don't think that there's an indication to use pharmacologic intervention.

Dr. Webb: Now, if they're hypoactive but they're psychotic and the family ... Like they're seeing things, hearing things, and they appeared distressed, they're not agitated but they're distressed by psychosis, that might be a time to intervene with some low doses of the medication.

Dr. Webb: And again, what's not clear, and like this trial from the New England Journal, they're able to screen and identify patients that had delirium, the degree of distress that you're then assessing at the bedside or how symptomatic that patient is from the delirium. There wasn't sort of a quantitative assessment of severity. And so the question sort of becomes, I think that's where the art of

doing this is different than sometimes the science, is we're often times at the bedside assessing how symptomatic that patient is.

Dr. Webb: So I don't think cart blanche that if you identify delirium, because we believe is psychoactive that we treat that with medication. So we can try to do non-pharmacologic interventions, help with sleep/wake reversal, and find ways that we can try to reverse that.

Dr. McPherson: Sure.

Dr. Webb: But if a patient's frankly symptomatic and psychotic, and we often times associate much more symptomatic delirium with patients that are psychotic and agitated 'cause that jumps up and kisses you on the lips. You see that, it's shocking, the nurses are distressed, the family's distressed. And so we tend to rise to making pharmacologic decision at that point. But I think it's harder with hypoactive delirium.

Dr. McPherson: I agree. But speaking of the hyperactive delirium, as you just mentioned, where the patient is clearly frightened, or perhaps harming themselves, or at risk to harm other people, and the family's very upset, the nursing staff's upset. I know that we certainly try to maximize reorienting people 'cause we've certainly had a lot of literature in the last couple years, that ... you mention Haldol you'd be burned at the stake. Especially in a nursing home, especially in a delirious dementia patient. What do we do? Do we tempt the fates and try to use Haldol? Do we reach for Valproic acid or carbamazepine? What are your thoughts on this?

Dr. Webb: Yeah, so again I think the primary upfront conversation with everybody in the family is what the goals are. If the goals are try to help manage the symptoms, then I think we try to identify how we attack those symptoms. And so if they're psychotic and we think that there may be a response to an antidopaminergic agent, then try that. I think if you're in a ... Where we run into some of the bigger issues are still facilities or other long term care facilities that have policies to try to avoid using those agents at all costs. I think often times in that situation, again trials of medications to try to help with sleep/wake reversal, like melatonin or even trazodone may be helpful. And then honestly in that setting I tend to use all pro eight. Again, typically go low and slow, so 250 or 500 at that time they start with and then potentially divide that does BID. And then ... And trying to use some of the sedating effects of that to help with the behavioral symptoms. And that tends to be my kind of primary drug of choice if it's not an antidopaminergic.

Dr. Webb: But I think really it's trying to target those symptoms that are causing distress. And then providing a lot of education to the team and then to the family about the signs and symptoms at the end of life that can happen. Particularly that delirium can be part of that, and we have an obligation to manage those

symptoms and to try to help improve people's symptoms, particularly if it's an irreversible and/or [crosstalk 00:28:17], the real type of delirium.

Dr. McPherson: It can be a really difficult situation though, particularly in a facility like a nursing home or assisted living, where the family can't be there 24/7 and the facility doesn't have the staff to sit there and provide a compassionate presence for the patient. And you do feel guilty reaching for a drug for that purpose.

Dr. Webb: Right.

Dr. McPherson: But it can be very challenging I think. Don't you?

Dr. Webb: Yeah, it's very challenging I think, particularly for families that have the ability to be at the bedside, a cognitive anchor. And I often times refer to families as it's extremely important. It's a lot of facilities, yeah it ended on Frankfurt, we get into a bond, and in order to help teams manage symptoms ... Especially when the caregivers are recognizing that someone is suffering and is having a lot of symptomatology. I think there's always that tender balance-

Dr. McPherson: Sure.

Dr. Webb: Of trying to maintain the ability to do those interventions that are nonpharmacologic or otherwise, rather than ... I think there was a shift for a long time. You know we talk about the pendulum swings where various medications were used inappropriately, and I think the recognition that there are other ways of doing this ... And hopefully things like [inaudible 00:29:30] and others that bite. Those cases in Parkinson's disease might be the alternative again, though wildly expensive and probably harder to access in that setting.

Dr. Webb: And I think in some ways too, sometimes those diazepines might be an option. I know there were always concerns about causing some paradoxical reactions, but I think in some settings, some patients do respond to those agents, even at such low dosages, so that can be a long term alternative.

Dr. McPherson: And that is an issue, because I've always taught people that benzos can actually make delirium worse or precipitate delirium. And the other day I was having a lovely conversation with the hospice nurse, and we have a comfort pack or a starter kit, a little box with a few doses of several medications, which includes Haldol and lorazepam often. And I said, "Well how do you decide or how do you teach the family to decide whether to give the benzodiazepine or the antipsychotic?" And she's like, "Well, I don't quite know. I tell them if the patient's agitated-" I said, "Are you referring to motor agitation?" She says, "Yeah, then I would tell them to give the benzo, but if they're really agitated like try to take a swing at somebody or seeing things that aren't there, hallucinations and so forth, then use the Haldol."

Dr. McPherson: What do you think is the best advice to give a hospice nurse in that area?

Dr. Webb: Yeah, that's always a challenge, and that was one of the hardest parts of being a hospice Medical Director and taking a phone call in the middle of the night who was out seeing a family about how to manage those symptoms. And this is the day to day work that our hospices and families are trying to sort of navigate.

Dr. McPherson: Right.

Dr. Webb: I think that the conversations that I've had, and it's in some of the literature, that in general Haloperidol is not that sedating. It can be for some people, but I think again if the goal is that you're trying to ... particularly when a family or a caregiver's in danger of being harmed because again, somebody's psychomotor agitated and you need to really calm that behavior down, then sometimes then I'll recommend trying the haloperidol up front. And then if that's not working, particularly if there's any risk of causing apathesia, or worsening that motoric symptoms, then I think we're sort of adding in some lorazepam.

Dr. Webb: And I think there's some studies that have been coming out, particularly for folks with cancer toward the end of life, that that combination may be more effective so maybe we use higher dosages than we'd thought about using in the past. But I think it just depends on the patient population.

Dr. McPherson: And I think this leads us to our last question. Dr. David Huey's work, from MD Anderson, he did show that benzos may have a role in delirium. Which again, does fly in the face of a lot of what we've learned and teach other folks. So you alluded to the fact that a benzo may be appropriate. So what do you make of his work and how would you characterize that?

Dr. Webb: Yeah, so David's study was really, really interesting. You have a sort of very specific patient population, and I think again sort of lends to the subtleties and how we choose dosages. So his trial, which was patients with advanced cancer, at the very end of life, we're talking hours to days, who developed agitated delirium, they looked at treating patients with either two milligrams of Haloperidol alone and placebo, or two milligrams of Haloperidol plus three milligrams of lorazepam.

Dr. Webb: And their primary outcome in the trial was sedation, so Richmond Agitation Sedation score, I believe it was minus two to minus three. And what they showed was that the combination of two milligrams of haloperidol plus lorazepam was effective in achieving that RASS score within about 30 minutes, it was durable out to about eight hours. And interestingly what they also showed, and I think what a lot of people would be concerned about using that high of a dose of that benzodiazepine, was that there was no increase death in the arm that got lorazepam. So they didn't sort of hasten death at the end of life in those patients.

Dr. Webb: But the caregivers and the nurses that were caring for those patients showed significant improvement in their interpretation and comfort of those patients at the end of life. And So I think what's really important about this is that ... Again, these are cancer patients in the last hours or days or life with agitate delirium, and in that setting this suggests that that higher dose of the benzodiazepine could be and can be effective in combination with two milligrams of haloperidol.

Dr. Webb: Or [crosstalk 00:34:03] maybe we have to be really careful with, is that people don't extrapolate this to other patients, because I think if you had a patient, like an octogenarian with dementia come into the ED who's had a UTI with agitated hyperactive delirium, and you gave them three milligrams of lorazepam ... You know, aspiration much?

Dr. McPherson: Mm-hmm (affirmative).

Dr. Webb: I think we're gonna have major problems. So we have to be very careful with that data. And we actually just had a journal club here with our Gyn/Oc colleagues where we talked about the trial really to highlight the role that it could play. And we continue hammer home the fork in the road of where you've got patients who are really benefited palliative intervention, where the goal is symptom management that may be comfort over consciousness, that this could be used primarily to achieve sedation for patients who are really agitated at the end of life. Versus somebody who may have a reversible delirium where you need to do a good medical work up, you would not want to give three milligrams of lorazepam.

Dr. McPherson: Sure. Do you think it hastened death?

Dr. Webb: No. At least in the trial it didn't. And I think the challenge that we would have to do in the real world, and I think what they didn't talk about so much in the trial was ... In combination, particularly if you have patients who are on higher doses of opiates, and in combination with that amount of lorazepam. So I think a lot of this is the pure decision making with families around being clear about what the intent of the treatment is. If the goal is to try to help improve symptoms. And then they often times, and I would say most clinical experiments, we usually try lower dosages of the agent first, just to see if it's gonna help. And I would argue that you should try a lower dosage first.

Dr. McPherson: Of course.

Dr. Webb: But I think part of this is, again, it's great to see these trials giving up better information about how to select specific patient populations. 'Cause I think five years ago without any of this data, we were just doing things based on guidelines and certain recommendations that weren't based out of a lot of good, randomized trial data.

Dr. McPherson: Right.

Dr. Webb: We're starting to get this information about how we can make better decisions. Clearly this helps us take better care of patients. And you're just taking care of the one patient that's in front of you. [crosstalk 00:36:21] Again, just try-

Dr. McPherson: But we just all need a Dr. Webb in our pocket though to do that. So I want to kidnap you and bring you home with me because you are so amazing. Is there anything else that you would like to add before we close out our podcast?

Dr. Webb: I just want to say thank you for bringing this to light, about having conversations about medications, and trying to provide better education to our colleagues. I think at any time it's always good to ask for help, and I would tell anybody at an institution if you've got a friendly private care doc or a friendly psychiatrist that you can ask questions about dosages, that's often times the best kind of strategy to get some assistance. So it's just the phone a friend. 'Cause that can be confusing, 'cause there's just so many medicines.

Dr. McPherson: Wonderful. And you promise to let me do a podcast with you once a year right? For a little psych update, forever.

Dr. Webb: I promise. Yeah.

Dr. McPherson: No pressure. Well, thank you so much. I would very much like to thank Dr. Jason Webb who I think is just amazing and just so valuable, the information that he provides to all of us. So again this is Dr. Lynn McPherson, and this presentation is copyright 2018, University of Maryland. For more information on our completely online Master of Science and graduate certificates in Palliative Care Program, or for permission requests regarding this podcast, please visit graduate.umaryland.edu/palliative. Thank you.