Palliative Care Chat Episode 3_Interview with Jason Webb March 1, 2017

Lynn 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 to introduce our guest today, Dr. Jason Webb. Dr. Webb received his Doctor of Medicine degree from the University of Nevada, Reno School of Medicine. He specialized in internal medicine and psychiatry throughout his residency training and completed a fellowship in hospice and palliative medicine. He now serves as a faculty member in the Department of Medicine and the Department of Psychiatry and Behavioral Sciences at Duke University. He's also an associate program director for the Hospice and Palliative Medicine Fellowship Program at Duke University and director of education for Duke Palliative Care.

Dr. Webb, much to my delight, has agreed to discuss the very controversial publication titled "Efficacy of Oral Risperidone, Haloperidol or Placebo for Symptoms of Delirium among Patients in Palliative Care". Thank you for joining us Dr. Webb. We're very excited to have this opportunity to chat with you. Why don't we start by you kicking us off with an overview of this study?

Jason Webb: Well, thank you very much for having me, and I'm really excited to talk about this study as well. So this was a really exciting study when it was published. This was a study performed at 11 different sites in Australia with a double blind, parallel arm dose titrated randomized clinical trial to assess the efficacy of using primarily oral liquid risperidone, liquid haloperidol versus a liquid placebo for a palliative care population of patients who were on inpatient hospice or in hospital-based palliative care service and to assess the role of using these two dopamine antagonist medications versus placebo on the symptoms of delirium and to assess outcomes to evaluate whether or not these therapies would eventually improve delirium for this patient population. Why this study is significant was that there hasn't really been any large randomized trials using these medications in a palliative-care population, which is why it rose to the level of being published in The Journal of American Medical Association.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: The clinical trial ...

Lynn McPherson: I'm sorry. Go ahead. Please, go ahead.

Jason Webb: The clinical trial is also interesting because they performed this trial over about a three-day period and, as we can probably continue to talk about, used a couple of different scales to assess the severity of delirium. Their outcome was essentially looking at delirium scores at the end of the three-day period. The primary outcome for the trial was essentially assessing the symptoms of delirium at the end of that three-day period. They had a few other secondary outcomes which they evaluated, such as severity use of rescue midazolam and side effects of these medications, such as extra pyramidal effects, sedation, and I think the thing that sort of caused this to be pretty controversial in our population, which was actually the survival of patients in this trial.

Lynn McPherson: Okay. Let's back up a second. We're living in this era where we see long-term care facilities in the United States have signs in the window saying, "We are an antipsychotic-free facility," which does not bode well for caring for terminally ill patients. With this study, what are your thoughts about their selection of these particular two dopamine antagonists, Risperdal and haloperidol? Do you agree with those selections and comparing them with placebo? How do you think they made the decision and can we make these sweeping conclusions based on that decision?

Jason Webb: Yes, so this is actually one of my biggest pet peeves about this trial. I think that they selected these two dopamine antagonists, and I'm actually selecting my language really specifically. I'm going to refer to these medications as dopamine antagonists and not as antipsychotic. Part of that is because as a psychiatrist, these medications are not created equal, and when we use the [inaudible 00:04:04] term, antipsychotic, I think it gets thrown around. This class of medications are classed as, if you look at, depending upon how people label them as first generation, second generation, typical versus atypical, they're actually quite different. In looking at this and comparing placebo, and the way they did this trial was they compared risperidone to placebo or haloperidol to placebo. These two drugs are primarily strong dopamine antagonists with very little other primary receptor antagonisms. Other drugs in the dopamine antagonist class can have variable effects. Take, for example, quetiapine, which has a strong antihistaminergic effect or sort of sedative effect to the medication ...

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: Versus something, say, like olanzapine, which has some potent antidopaminergic effect, but also has strong antihistaminergic and some strong anticholinergic effects and some strong antiserotonergic effects ...

Lynn McPherson: Uh huh.

Jason Webb: Which is part of the reason why that medication is frequently used in our population for things like nausea and vomiting. In looking at this trial, really they picked two drugs that were pretty biosimilar, meaning that they both blocked dopamine without a whole lot of other effects. They're not particularly sedating medications. Getting to your point about this facility is "antipsychotic-free," I don't actually know what the heck that means, because there is just sort of a whole host of these medications and so in the selection for this trial, what I think is a major critique is that you actually compared essentially two drugs that were pretty much the same.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: I don't really know what to do with that in some ways. It would have been much more robust, in my opinion, to have compared haloperidol, which is sort of the standard medication we often times use for delirium and palliative care or hospice population, versus something like quetiapine or olanzapine or even chlorpromazine, just given the different pharmacology, particularly the antihistaminergic effect of sedation. I think that's been one of the large critiques here is that they picked two non-sedating antidopaminergic medications ...

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: Where it would have been more interesting to compare, say, haloperidol again against quetiapine or olanzapine.

Lynn McPherson: Mm-hmm (affirmative). Well, you did speak a little, but you referenced this a little bit earlier. Speaking to the outcome measure, did they pick the best delirium-rating tool? Is it even validated? Did they use it at the most appropriate point in time? This is a very brief trial.

Jason Webb: It was a very brief trial. Again, they took patients at sort of their baseline up to 72 hours. Interestingly, they used sort of two different tools for assessing delirium and the one that was their primary outcome measure was the nursing delirium screening scale, which inherent in the name is a screening tool. This was actually validated in the trial that was published in 2005 in the Journal of Pain and Symptom Management. The validation population that this was used in was a Canadian-based inpatient hospital population. It was sort of a heme/onc/internal medicine inpatient population, particularly of cancer patients. One of the questions is this

was validated at an inpatient hospital-based population, but they weren't particularly specific in the trial when they validated this. Let's say that this was sort of the same population that was used, say, in this trial, which is a little bit hard, to be honest, for the study ...

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: Authors to pick a validated screening tool in a haloperidol population, but this is what they used for screening. What was interesting in the way that they chose this, was that their outcome was dependent on looking at sort of three sub scales from this, which was inappropriate communication, inappropriate behavior, and if patients had illusions or hallucinations.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: The way that this scored is you get one point ... There's sort of a two-point measure scale, so 0 they don't have any symptoms. 1 versus 2 are mild or severe.

Lynn McPherson: Right.

Jason Webb: This is done over sort of three different time points. The trial was designed essentially if they scored 1. If they got a 1 on that, they scored positive and that was an indicator that they then get medication.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: Well, I mean, any palliative care patient who has delirium, which really this is a symptom that the brain is failing. It's a sign of brain failure and organ dysfunctions. Patients are dying. They're probably going to score 1 on likely one of those three different subsets.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: Now, they chose those three based on sort of a cohesion of the palliative care doctors, the geriatricians, and the geropsychiatrist that looked at this and said, "Well, this is the best we can do because there's really no validated, agreed upon, primary outcome measure for delirium symptoms in this patient population." This is sort of what they thought was like their best option.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: It sort of brings to question, was this the best tool to use as their primary outcome. They, I think, sort of tried to make up for that by using the MDAS, or the Memorial Delirium Assessment Scale, which is severity scale. It's not a screening. It just looks at how severe are the delirium symptoms. That has a bit more of sort of broad assessment across the delirium literature, but from a screening assessment, the new desk isn't quite used as much. I mean, the CAM, or the Confusion Assessment Method, is a much more robust sort of ...

Lynn McPherson: Right.

Jason Webb: The medically-ill population used screening tool. There's a little bit of controversy about whether or not this was the best tool to use, and particularly because their threshold was essentially just a score of 1.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: Really any patient with just a single abnormality in like their speech, their cognition, their behavior, would have been given a dose of one of these antidopaminergic medications. Their threshold for treatment was pretty low.

Lynn McPherson: Mm-hmm (affirmative). This is really scaring people, this trial. People are reading that ... People that got Haldol died sooner. The people who got Haldol used more midazolam. Were these patients even randomized equivalently in your opinion into the three arms? Can you speak to the mortality difference with the haloperidol specifically?

Jason Webb: Yeah, so that's a really good question. I think that's been the thing that's been the biggest challenge to all of our palliative care practitioners. If you look at figure one in the trial, what's really interesting is that there are, on average, a little over 80 patients randomized to every single one of the arms.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: However, if you look at the patients in those arms, there was a pretty significant, though it didn't reach statistical significance in the number of patients who discontinued ... 37% of the patients in the risperidone arm actually discontinued the trial versus 22% in the Haldol arm. There was only about 17% in the placebo arm actually discontinued the trial. That was for a variety of reasons.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: What's important about that is that the trial was powered to have an end result of 55 patients participating in the study in the arms that received the antidopaminergics versus placebo.

Lynn McPherson: Uh huh.

Jason Webb: To be honest, I'm not actually sure that the risperidone arm actually achieved that based on the total number of patients that discontinued.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: Though because this was an intent to treat analysis, they could say that, yes, we had more than that number of patients ...

Lynn McPherson: Right.

Jason Webb: Achieve our, sort of, 80% A priority power.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: The problem is if you look at the way in which the overall population by characteristics is grouped, the challenge with the haloperidol group is that they're actually different than the risperidone group. They actually mention this in the limitations that was sort of buried a little bit later in the trial is that that population, particularly the haloperidol arm, had an older population, so more of the patients were over the age of 65 years old. They received about almost three times the oral morphine equivalent in the Haldol arm compared to the others. The average opiate, or the median opiate dose, was about seven, morphine equivalents for risperidone and about 33, of morphine equivalents for Haldol versus only 15 in the placebo group.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: Then on top of that, the patients that received the antidopaminergic medications were more likely to receive midazolam.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: If you step back, big picture, summarize that. You have patients who received haloperidol, they were older, they got more morphine

equivalent, as far as opiates during that three-day period, and they were more likely to get midazolam.

Lynn McPherson: Uh huh.

Jason Webb: We know that in a sick-patient population who get a lot of polypharmacy, like opiates, diazepam, these medications that their risk of dying is probably higher.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: It's a little bit tough to say that actually these populations were actually all the same. It's really difficult to, sort of, say whether or not those, sort of, maybe co-interventions with the midazolam or the fact that that patient population was potentially sicker or had a higher symptom burden to begin with, which may be an indicator that they were at higher risk for dying anyway, might have colored the overall outcome of the trial.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: I worry about that significantly based on the way the data looks.

Lynn McPherson: Yeah.

Jason Webb: The other thing that you don't see in the specific trial figures, but is in the supplemental e-figure, is that a lot of what they comment on is the delirium symptom scores. There's a figure one, that's MDAS scores of the delirium severity over the study period.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: What's really interesting is that the actual baseline delirium severity, if you compare placebo to the antidopaminergic arms, showed that actually the risperidone group and the haloperidol group just at baseline actually had a higher symptom score.

Lynn McPherson: Uh huh.

Jason Webb: If you follow those curves out, it actually makes it look like that the placebo arm had a lower symptom severity though, but hey started with lower symptoms to begin with.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: In some ways, at the very beginning of the trial, at its inception, the patients in the antidopaminergic arms were actually more symptomatic. So does that mean they were sicker? Does that mean that they actually were closer to the end of life because they had a higher symptom burden?

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: It's a little hard to extrapolate that, but I find that sort of curious that the patients initially randomized in the trial actually were more symptomatic when they started. Then, again, with this primary outcome that potentially, actually not the primary outcome, but the secondary outcome, that mortality was different. It's hard to interpret in the setting of higher symptom scores at baseline, more morphine, more midazolam, and that this is an older patient population.

Lynn McPherson: Having said what you just went through, which certainly seems like it skewed the deck to me, given these results, can we generalize the outcomes to "all palliative care patients, people with a serious illness, those that we typically see in practice?" It sounds like you don't think they really studied the representative population, or at least an equivalent population, across the three arms. Is that correct?

Jason Webb: I don't. I think part of this is sort of looking at the overall patient population that they started with.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: The majority of these patients were males with cancer and the majority of them were over the age of 65.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: If I have a patient who's under the age of 65, but, say, who has end-stage heart failure, if I'm on an inpatient hospice unit and I've got heart failure patients, patients with dementia, or end-stage Parkinson's disease, end-stage hypoxic respiratory failure, or from COPD, I don't know that I can actually generalize just the baseline population in this trial to an overall palliative care population.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: I think that makes partly the title of this trial a little bit misleading.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: The patients who were on a palliative care unit or a hospice unit, but they were really primarily cancer patients.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: From that standpoint, I don't know how to generalize other patients who might suffer from delirium.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: Again, that being said, it ...

Lynn McPherson: Go ahead. I'm sorry.

Jason Webb: It's also hard to sort of say, well, with my patient who comes in with, say, dementia, who's not receiving any opiates, who's under the age of 65, is that the same palliative care "population" of the study in this trial? I have a really hard time saying that this is entirely generalizable to my entire inpatient hospice unit just based on the data from this trial and their study population.

Lynn McPherson: Having said everything that you just shared with us, can you share what the take-home message should be for hospice and palliative care clinicians? Should we throw the antidopaminergic drugs out the window? Should we let the little old lady, who really thinks the boogey man is in the closet, suffer with that fear? How should we let this trial influence the way we take care of patients who often suffer from very frightening delirium?

Jason Webb: Yeah. Just to back up one second. Part of the take-home question here too is that when they randomized this trial, they excluded patients in the last week of life.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: At our hospice here at Duke, the average length of stay is less than a week.

Lynn McPherson: All right.

Jason Webb: The patients in this trial on average, in the placebo arm survived about, I think, it was 26 days versus those in the other arms were about 17 versus 16 days.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: This is longer than, maybe for a lot of inpatients in, say, hospices, where I think this is sort of added to the general population if you have a length of stay that's less than a week. If you a patient who has severe delirium, this trial actually, if you look at the outcomes, only included patients, if you look at the symptom severity scores, were mild to moderate.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: If I have a patient who is in, I think, the last week of life with severe delirium symptoms, accusations, psychosis, I don't think that you can apply this trial to the patients at all.

Lynn McPherson: Okay.

Jason Webb: These patients had mild symptoms and so I think for the bottom line in the take home, is that this is pretty specific.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: Patients were over the age of 65. Those who had mild-to-moderate delirium. Those whose life expectancy was longer than a week. Other patients outside of that, I don't think we can apply this to. Particularly, if you want to pick another medication, like if your hospice or your inpatient palliative care service wants to use a more sedating antidopaminergic medication, like quetiapine or chlorpromazine, ...

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: I don't know that you can apply this at all because they didn't use a drug that was biosimilar to those.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: Really I think the study tells us little bit about a specific patient population. I think it's a little bit ... Raises the bar that we need to have better symptom management science, particularly for delirium with this

class of medication and choosing treatment settings that seem appropriate for the types of tools we're using for screening.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: I don't necessarily think that this should cause us all to sort of just say that we should get rid of this entire class of medications.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: The accompanying editorial for this trial, I think, was actually a disservice because they jumped to conclusions about the role of these medications. I think there's a lot of skepticism that should be warranted in reviewing this and applying this to a "palliative care population," say on an initial consult service ...

Lynn McPherson: Uh huh.

Jason Webb: Or even if the patient who are in the last week of life.

Lynn McPherson: Mm-hmm (affirmative). For my little old lady who really thinks there's an alligator under the bed and she's a few days out from death, you're okay with me reaching for the Haldol, yes?

Jason Webb: Yeah. I think that, again, because they excluded patients who are in the last week of life and if a patient appears symptomatic and is distressed and delirium, for me as a clinician, that's akin to having severe pain.

Lynn McPherson: Right.

Jason Webb: It's a distressing symptom that's limiting a quality of life in their last days.

Lynn McPherson: Right.

Jason Webb: I would continue to use haloperidol to try to manage those symptoms.

Lynn McPherson: Oh, that's wonderful. Dr. Webb, we're going to look for you to design the next trial and set us all straight. Okay? Can we count on you for that one?

Jason Webb: I'll look forward to it.

Lynn McPherson: Any last comments, Dr. Webb? We're very appreciative of your time.

Jason Webb: Yeah. I think my last comment would be, with any of these trials when they come out, especially in a strong journal, it's always really important to sit down and kind of dissect what they did. Look at the study population. Look at the intervention. Look at the tools that they use to assess symptoms and what their outcomes are.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: Often times, we'll read a headline in a paper or hear about this at our national meeting, and it takes a little bit of time to do a deep dive into really what they did and who these patients are. It's really important because the word can get out that this could be a problem, ...

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: But the reality is that this was a pretty specific patient population with a short intervention over a couple of days.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: It's hard to really generalize this to, I think, our entire palliative care population.

Lynn McPherson: Yeah.

Jason Webb: One of the challenges in using these medicines is that they're not all created equal. If you look at really sort of the neuroscience of how these medications can be used, they're all quite different.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: It's really important to be a little bit skeptical about a really significant negative outcome, particularly also, I think the take home point is, that the mortality wasn't their primary A priority powered outcome.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: It was a secondary outcome.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: I'm not really sure that we can extrapolate that entirely to our patient population, so I wouldn't throw the Haldol out for anybody at this point. I think it just really brings to light the fact that we need more trials.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: Probably another trial comparing haloperidol to another medication, and then some cross comparison. Part of what this trial didn't do was compare the two medications against each other.

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: In a trial that actually has some crossover, or the ability specifically to assess two of these medications, particularly one that's more sedating against haloperidol, ...

Lynn McPherson: Mm-hmm (affirmative).

Jason Webb: I think would give us a lot more information.

Lynn McPherson: I think you're ...

Jason Webb: I ...

Lynn McPherson: Well, thank you so much for your insights. I know this trial has really rattled the cage of many a hospice and palliative care practitioners. I've even heard a whole healthcare system saying, "That's it. No more antidopaminergic drugs for delirium." It's good to shed this light on this.

I'd like to thank our guest, Dr. Jason Webb, from Duke University. Such an insightful conversation. Thank you so much. Thank you for listening to the Palliative Care Chat podcast. This is Dr. Lynn McPherson and this presentation is copyright 2017 University of Maryland. For more information on our completely online Master of Science and Graduate Certificates in Palliative Care, or for permission requests regarding this podcast, please visit graduate.umaryland.edu\palliative. Thank you.