

University of Maryland, Baltimore Presents

Palliative Care Chat: Episode 4

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Description: In this episode of Palliative Care Chat, Dr. McPherson interviews Dr. Meera Agar and they discuss Dr. Agar's published work entitled 'Efficacy of Oral Risperidone Haloperidol or Placebo for Symptoms of Delirium Among Patients in Palliative Care.'

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 Certificates in Palliative Care from the University of Maryland, Baltimore. I am so excited to introduce today's guest, Dr. Meera Agar, Dr. Agar, or Professor Agar is a palliative medicine physician with a particular interest, as you'll see, in the supportive care needs of people suffering from advanced illness on the brain.

Dr. Agar leads a clinical research portfolio at University of Technology, Sydney, Australia. Including clinical trials and health service evaluation. She led a world first clinical trial of anti-psychotics and delirium, which we'll be discussing today. And is leading a NSW government-funded trial of the use of medicinal cannabis for the terminally ill. A fellow of the Royal Australasian College of Physicians, fellow of the Australasian Chapter of Palliative Medicine and Clinical Scientists, she holds a Master's in Palliative care. Her doctorate was awarded in the area of delirium and advanced illness. And she's won numerous awards and honors.

So Dr. Agar, thank you so much for joining us today, and as you know we'll be discussing the paper that you were first author on titled, 'Efficacy of Oral Risperidone Haloperidol or Placebo for Symptoms of Delirium Among Patients in Palliative Care.' Impressively published in JAMA Internal Medicine.

So can you start off by telling us your impetus for doing this study?

Dr. Agar: I think really the impetus was that we saw such a need in terms of the clinical care, of people with delirium, the distress that the delirium symptoms causes, but the evidence best to actually inform how we can prescribe in clinical practice or how we can make a difference for care for people with delirium in the palliative care setting, was very scarce and we wanted to really answer a real world question that affects all of our clinical practice in a day to day basis.

Dr. McPherson: Yes I think it's a very practical question, it seems to be quite a pervasive and often very frightening symptom. So can you briefly describe for us your methods for this study?

Dr. Agar: So we undertook a randomized blinded trial. And really the fundamental question was to look at anti-psychotics in particular two agents which are able to be given in an oral route, risperidone and haloperidol. And we were comparing those both with a placebo to look at whether they reduced distressing symptoms of delirium in people receiving palliative care. And really

we tried to mirror the approach that's used widely in clinical practice. And it's very aligned with the guidelines in delirium care, which really suggests that the use of medication should be tailored for symptoms that are causing significant stress.

Dr. McPherson: Mm-hmm (affirmative).

Dr. Agar: Yet the trials and the search to-date haven't really tackled that question from that perspective.

Dr. McPherson: Mm-hmm (affirmative). It doesn't seem to be one size fits all, certainly a managing delirium, we'll certainly agree there. I'm curious what kind of response you have observed from the palliative care and the geriatrics community. Since this paper was published I think everybody around me has held their head and said, "Oh no what do we do now?" What have you experienced?

Dr. Agar: So I think before we started the trial, I think there was true equipoise, that there was such a wide variation in clinical practice and views, so the clinicians who really don't feel that there's any role for these group of medications in the management of delirium period. There's a group that were telling us that they use it in very tailored situations in the group, that had the much broader use, for a much wider range of symptoms. So we really entered the trial with true equipoise that we didn't know which of the [arms 00:04:07] would be the best option.

I think there are people who are now responding to us and saying, "Well, now that's very aligned with what our practice was anyway. The trial isn't changing what I do to the groups," with they either had a targeted approach to the use of these medications or those who had a much broader approach who are finding that they have to think about how these results inform their practice.

Dr. McPherson: Mm-hmm (affirmative).

Dr. Agar: But I think the most critical thing to us is that this is bringing discussion about delirium care, research into trying to improve delirium care for people in palliative care to the forefront on a hope that this is not the end of the discussion. I hope this is the beginning of a rapid escalation in the research to help us tackle lots of really complex-

Dr. McPherson: That would be wonderful, certainly. I share your opinion for what I'm hearing here, that it's not an all or none sort of thing, it's not black or white. I despair when I see nursing homes in the U.S. often put up a sign saying, "We are an anti-psychotic free facility," and I just don't think you can take a big old paintbrush and paint the whole scenario with that. What are your thoughts on that?

Dr. Agar: Well I think with any medication we actually need to really go back to those principles in terms of what is the biological plausibility for this medication, for these symptoms? Assess the pathophysiology and I think the area of delirium pathophysiology is rapidly evolving and the role of those remain in the big picture is rapidly becoming smaller in the areas of neuro-inflammation, glucose metabolism. Increasingly are becoming much more important in our understanding of delirium.

Dr. McPherson: Mm-hmm (affirmative).

Dr. Agar: And so working out what it is we're targeting in the path of physiology, how that might impact on symptoms, and then designing trials that actually evaluate that really specific question and I think we have to think about delirium care in that really biologically based way.

Dr. McPherson: Mm-hmm (affirmative).

Dr. Agar: And we've asked the particular question but there are several others that need to be answered to help us understand that more.

Dr. McPherson: Absolutely-

Dr. Agar: And then we put all of that evidence together and apply that with particular clinical scenario in front of us.

Dr. McPherson: Yes.

Dr. Agar: And some of those situations may be refractory or fall outside the evidence-

Dr. McPherson: Mm-hmm (affirmative).

Dr. Agar: But I think the actual issue we have for delirium care is that there's such a void of evidence that too many clinical scenarios fall into that group and I think we have to do better from that perspective.

Dr. McPherson: Parsing it out, so to speak. And some people have looked at your study and said, "This is a very particular type of study, most of your patients had cancer, they were within two to three weeks of death, they were not like imminently dying. So really is it applicable to a wider population? Perhaps patients who are within several days or a week of death who have even more severe delirium." What are your thoughts about that?

Dr. Agar: Well I think it come to the biological plausibility, is there a biologically plausible reason for why delirium, in someone who's in their last hours of life would be different to this group of people. And my view is that probably there isn't suddenly a completely different pathophysiology in question, but I think we need to do the further work to actually establish whether-

Dr. McPherson: Yeah.

Dr. Agar: That is the case.

Dr. McPherson: And I certainly agree that nonpharmacological interventions are best if that will get the job done, but we do see in people very close to the end with very frightening delirium, what's the best option? I agree we need more research but you take care of patients very often I'm sure, what do you do in those situations?

Dr. Agar: So far as we've been doing this trial and I think the benefit of doing a trial is that you get to speak to a lot of clinicians who are tackling this issue on a day to day basis, by doctors, nurses, pharmacists, the whole interdisciplinary team, this affects everybody. And as we were doing the trial, I think what we really began to understand is that sometimes it is symptom recognition rather than the word delirium is not used often enough.

Dr. McPherson: Mm-hmm (affirmative).

Dr. Agar: A full assessment of the etiology of delirium is often not put in place and the most critical thing is that communication with the families and the patient if they're able about what delirium is. Demystifying what it actually is and why it's happening, and providing support and empowering a group of strategies around that person is so often missed. And I think we often call situations refractory when some of those really fundamental things haven't been put in place, so. I think we're challenging people to think about, do you people have in their units, or in their services, systematic ways to make sure that happens to every person with delirium.

And that becomes core business not just now and again when people remember.

Dr. McPherson: I was interested to read in the accompanying commentary by Drs. Maust and Kales they said that, the title of their article is 'Medicating Distress,' often they postulated we use these drugs to make ourselves feel better. What do you think about that?

Dr. Agar: I think in some situations when people take very narrow patient recognition and then haven't taken time to sit down and have that conversation. No I think Karen Stein Hauser's work from the 2000 paper, we underestimate how mental awareness and being aware how critical that is. And I've had many patients say to me that now that they understand what is causing their delirium symptoms, they really, they want the management to be focused on being mentally aware and sedation or something that may lead to some sedation is not a treatment that they would concede of. So I think we have to tailor it to every individual and essentially all our prescribing in delirium is off-label off-license prescribing.

Dr. McPherson: Mm-hmm (affirmative).

Dr. Agar: And I think it's about the informed consent discussion with the best available evidence we have and then tailoring it to that individual.

Dr. McPherson: Mm-hmm (affirmative). I agree. Were you at all tempted to look at any anti-psychotic agents that were more pharmacologically distinctive? Because haloperidol and risperidone are fairly similar, were you tempted at all to look at an older drug such as chlorpromazine? Or I think the number one drug in the U.S. now is quetiapine, which I see prescribers using off-label very often as a sleeping agent.

Dr. Agar: Yep.

Dr. McPherson: What are your thoughts about different agents?

Dr. Agar: So this trial arose out of a legislative and policy framework in the Australian context which was about improving access to medicines for palliative care patients. And so there was a program of consultation with the Australian clinical community around the medications that they felt there was difficulty accessing or the evidence that underpinned access within the current frameworks in the Australian medicine sort of legislative framework were not available. So risperidone was one of those medications that was identified. And so we felt that because haloperidol actually is a much more commonly used medication in this scenario, we added the third on. There was also the practicality of the blinding, both of those can be made into an oral solution. So we would've had to have several placebos if we had, and we were a bit worried about the swallowing issue and so the oral solution was a partly a pragmatic-

Dr. McPherson: Mm-hmm (affirmative).

Dr. Agar: Decision as well. So I think it was-

Dr. McPherson: Okay.

Dr. Agar: Some of those drivers in some of the pragmatic decisions and the policy framework that led us to those two agents. But I agree that understanding that biological basis of the choice of agent and there are some questions that remain around the different receptor-

Dr. McPherson: Mm-hmm (affirmative).

Dr. Agar: Blockades of some of the other agents that would be interesting.

Dr. McPherson: Yes, I agree, just like some patients respond better to one opioid to another. You have to wonder about the responses to individual antidopaminergic agents as well. Some people have questioned that in your trial, the two active drug

treatment arms perhaps may have been a little bit dissimilar even if not statistically from the placebo arm. For example the Haldol group was a little bit older, they were using more opioid baseline and they ended up using more midazolam. What are your thoughts on, if any influence it had on the outcomes or not?

Dr. Agar: So they weren't statistically significantly different in the models when we accounted for those baseline variables and the results didn't change. In terms of the midazolam dose, the actual overall use was low, so there was many people who didn't receive any midazolam at all. And we then also looked at so the groups that did receive midazolam, there was no difference in the medium dose that was received, across the arms. So there doesn't seem to be any inequity in terms of the dose exposure.

Dr. McPherson: Mm-hmm (affirmative).

Dr. Agar: And though the amount, the percent that received that dose was slightly higher in the haloperidol and risperidone arms.

Dr. McPherson: Mm-hmm (affirmative).

Dr. Agar: I think the challenge and for anyone who's designed a trial, the ethical issues in both the palliative care population, but if you add delirium and cognitive impairment and a trial where the proxy is consenting.

Dr. McPherson: Yes.

Dr. Agar: After much sleepless nights in discussion, you can imagine that leaving the groups without a rescue we felt was not warranted, but you could argue that that adds another challenge. But that was the reason we came to that decision.

Dr. McPherson: I'm sure getting this through institutional review board was a nightmare, especially when I see you had 11 different sites. And as you mentioned, it's a fragile population and you're using psychoactive drugs, I'm sure that was a real day at the beach getting that through. I'm curious why you only [crosstalk 00:15:18] I'm sorry.

Dr. Agar: We had to actually present it to the guardianship tribunals, which are the bodies that look at proxy decision making for clinical care. And the interesting thing was there were two lay members on both of those reviews and the overwhelming comment was that people with delirium deserve the best quality evidence to guide their care and they were very encouraging. So I think that gives us all encouragement that trying to do a studies that tackle questions in delirium should be done and that the community and our consumers are really supportive of that.

Dr. McPherson: Absolutely. I tell my students that when you consider how old the field of palliative care is, relative to the field of internal medicine, I think just during my career, it's been astonishing to see the evolution of evidence that has been published. Would you agree?

Dr. Agar: Yes. [crosstalk 00:16:11]

Dr. McPherson: But still a lot of work to, granted.

Dr. Agar: Tackling questions that are so important and mirror what we have to tackle in clinical practice which I think is the exciting part.

Dr. McPherson: Yes I love practical research. I'm curious why you chose to only follow these patients for three days.

Dr. Agar: So I think, our approach was really that if you are going to use a medication to treat delirium. In this group of people, we want a response from it, because we're treating distress and that was our primary question. That we felt that if we weren't seeing responses within a three day period, that that from a clinical perspective would be not a really, effective strategy for that clinical problem.

Dr. McPherson: Mm-hmm (affirmative). Okay. And any thoughts on the cause of death? I tried to think of why it would be, and the only thing that came to my mind was prolongation of the QT interval for glucose intolerance. But I didn't think glucose intolerance at least in my mind would so quickly have an effect. What are your thoughts?

Dr. Agar: So I think the challenge is that we have overall survival outside the study period, but we don't have any medication exposure, data or whatever clinical events happened to these people to really look at all the covariance that might be influencing mortality. So we don't know how many had an initial resolution of their delirium and then had a second episode. We don't know what the treatment choices of the clinicians after the study period were to know what the exposure to both the agents within the trial, but other anti-psychotics or other psychoactive medication. So I think that truly a hypothesis generating a secondary outcome which we need to really understand a bit better.

Dr. McPherson: I agree. So what are the next steps for you? What's next on your dance card?

Dr. Agar: So I think we're keen to try and look at system approaches to improving delirium care and in the more holistic sense. I think having an ongoing conversation about a delirium care. And I think trying to understand whether there are novel targets and agents that would have a much better chance of making fundamentally major differences in outcomes for people with delirium both in palliative care but also delirium outside of palliative care.

Dr. McPherson: Mm-hmm (affirmative).

Dr. Agar: Is something that we would be really interested to see.

Dr. McPherson: Oh that's great. Any final thoughts you'd like to share with our listeners about this trial or anything else in your practice and research?

Dr. Agar: I think just to encourage people to be involved in research that explores care for people with cognitive issues in delirium in palliative care. It may be challenging, but work collaboratively with people that are working in this area. But also who do delirium research outside of palliative care and I think if we all put our minds to it and are passionate about why this is so critically important. We can really make big in roads in trying to understand how we can care for these people better.

Dr. McPherson: Oh that would be awesome, that would be tremendous. Well I'd like to thank Professor Agar from the University of Technology, Sydney, Australia. I think we should have our next meeting at her house, she has an adorable accent. It's just been so interesting speaking with you. So I'd like to thank everyone 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 Masters of Science and Graduate Certificates in Palliative Care, or for permission requests regarding this podcast. Please visit graduate.umaryland.edu/palliative. Thank you.