

Dr. Lynn McPherson:

This is Dr. Lynn McPherson and welcome to Palliative Care Chat, the podcast series brought to you by the Online Master of Science, PhD and Graduate Certificate program in Palliative Care at the University of Maryland. I am delighted to welcome you to our podcast series titled Founders, Leaders and Futurist in Palliative Care. A series I have recorded with Connie Dolan to support course work in the PhD in Palliative Care offered by the University of Maryland Baltimore.

Hello everyone, this is Lynn McPherson, I'm the program director of the online master of science graduate certificate and PhD in Palliative Care at the University of Maryland Baltimore, we are super duper excited about our program. So as part of that effort we are recording a series of podcasts on Founders, Leaders and Futurists in Palliative Care. And helping me with this whole thing is my good buddy Connie Dolan, who is an advanced practice nurse who really helped shaped the role of advanced practice nurses in particular but really has had a tremendous influence on the whole field of palliative care and it's evolution. And Connie teaches in the first course in the Master's program, she was the first person I called and then when we're very close to the final approval of this PhD, she was the first person I called here as well, so she will be co-teaching the first course on Understanding Palliative Care and Building Blocks for the Future and of course on Leadership in the program. So she's helping me with all of these podcasts.

And we're very excited about our guest for this episode Dr. Mellar Davis who is the head of Palliative Care for all of Geisinger. Welcome Dr. Davis, how are you?

Dr. Mellar Davis:

Thank you, thank you for having me on.

Dr. Lynn McPherson:

We are super excited you're here and I've known you for many years, mostly from... Well where I met Dr. Davis is I was attending a Palliative Care program I don't even remember, oh I think it was one of the Academy meetings, AHBM and I think it was a pre-conference that Dr. Davis was doing with Dr. Declan Walsh and they were talking about where Dr. Davis worked at the time, Cleveland Clinic, their approach to opioid dosing in a variety of circumstances, acute pain, chronic pain, conversions and so forth and I was beside myself because I was in the throes of writing the first edition of my book on opioid conversion calculations and I know that I monopolized Dr. Davis, during every break, I was a stalker, I'm very proud of that and it's been the start of a beautiful friendship. I appreciate you so much. So Dr. Davis why don't you tell us, I know you trained as an oncologist and I know you phoned the wife one day and said, "Guess what, I'm going to jump on this new pony called Palliative Care." Tell us about that.

Dr. Mellar Davis:

Yeah, I finished my hematology oncology training at the Mayo Clinic in 1982 and I had about 17 years as an oncologist hematologist and realized that when I was managing patients with cancer, they had symptoms that I couldn't handle, that I was really not trained to manage and so I was looking for resources, teaching. And palliative care in the United States, there were no accredited fellowships so I contacted Robert Twycross, and he said in 1996 come over but come over for two weeks and see if you like it, see if you like it and so I came over and rounded with him and I was floored by what they could do pharmacologically, symptom wise and psycho socially with patients without giving chemotherapy and getting patients feeling better.

So when I came back to the United States I was really quite changed and so I elected to go back in 1997 and spent the summer practicing with Robert Twycross and that was quite an experience. I don't know if you, probably not very many people have rounded with Robert Twycross or is still around that rounded with him, but he was meticulous. He was meticulous pharmacologically. And there were several components to that, that he was really very gifted in.

Number one is managing symptoms with the fewest number of doses per day, because that had something to do with compliance. So if you could give sustained release morphine twice a day it's better than every four hours so to speak, so we would go over the medical lists of patients each day. Number two is that if you made a suggestion he would take it but you needed the data to be able to convince him. It wasn't just an opinion. So you had to have chapter and verse to be able to influence how he was thinking, he had an inquisitive mind, he was not only brilliant but willing to learn, willing to learn from anyone as long as you could present the data to him that would convince him that, that's a proper approach to managing those particular patients. And so we would go over the list of medications every morning, we would sit down in rounds and go over that and the other is to extract things that were not needed.

And that was really the beginning influence of palliative care on me, was to see how he managed patients, the pharmacology was extremely important but also the bedside approach and rounding, you sat at the bedside or you kneeled at the bedside, you never really stood over a patient. That was there and so you rounded on a regular basis for it and it was a comprehensive service in that not only did they have an inpatient unit but they also had a community based program with the McMillan nurses. But they also had daycare, something that we don't have and I would often round in the daycare area, where patients would be dropped off, they could socialize and things like that, they would look at their medications, if they needed transfusions they could get transfusions there. So there were a lot of things that could be done in his center which was really a relatively comprehensive center.

So when I came back to the United States I was really enthralled with the pharmacological management and one of the first things I faced was a woman who had ovarian cancer and had a bowel obstruction and she did not want anything done, and she wasn't a surgical candidate, she didn't want anymore chemotherapies but she wanted symptoms to be managed. And what we were doing in Oxford was to use hyoscine butylbromide, morphine and haloperidol and you could mix them together as a single infusion and give it to patients as a syringe driver and you could send them on their way and control their symptoms.

The interesting thing is that in conversing with them and looking, and with actually a pharmacist, Anne [inaudible 00:07:26] we found that glycopyrrolate was also a quaternary scopolamine derivative, so it wouldn't cross the CNS, it was as affective as hyoscine butylbromide so we mixed this in with morphine and haloperidol and we found a hospice that was willing to take it as a mixed in a single infusion, and she went home and comfortably died about two weeks later. Her husband came back and was extremely grateful because they could get closure, she could be around her friends and things like that.

But as I was discharging this patient my intern came up to me and said, "Well you haven't done anything for this patient." And what that intern meant was that I had not treated her cancer nor taken her to surgery. So it was really an eye opening experience.

1999 there was a position opened at the Cleveland clinic and it was Cicely Saunders third research fellow Declan Walsh who had been at the Cleveland clinic since 1989, that invited me to come up, I went up several times and eventually moved there in 1999 and I did both oncology and palliative medicine and that was actually quite freeing. Because I found that as an oncologist having palliative care skills and growing palliative care skills I didn't really need to treat someone with chemotherapy. I had a

lot more tools in my toolbox. So I eventually elected to do advanced lung cancer, because it was both a great palliative group of patients to deal with but also there was chemotherapy that could be used so it was a very freeing experience.

And eventually I elected to do full-time palliative care before leaving there. And while I was at the Cleveland clinic we got interested in the structure of palliative care and it's finances and we had the ability to do some of that work while we were there and then we had some real interest because there's some basic science research there we got really interested in fatigue. So we did this translational work looking at cancer related fatigue, looking at EEGs, EMGs, transcranial magnetic resonance and things like that and we were able to find that for instance that cancer related fatigue was a central phenomenon, just like anorexia is a central phenomenon, it's really a central phenomenon that occurs with that.

I also led the fellowship for about eight years and had the opportunity of training and doing qualitative research with the fellows but it was a great environment not only for practice but also learning research skills under a fairly well known palliative care researcher, Declan Walsh.

So my exposure and the reason why I have such an interest in pharmacology is my initial exposure was with the first research fellow of Cicily Saunders, Robert Twycross, and the third research fellow, Declan Walsh, both of them very good pharmacologists, very thoughtful individuals.

Dr. Lynn McPherson:

So how did Dr. Gav fit into all this?

Dr. Mellar Davis:

Dr.?

Dr. Lynn McPherson:

Gavril Pasternak?

Dr. Mellar Davis:

Oh Gav. Gav? While I was at the Cleveland clinic Declan sent me off to look at opioids, so hence the two books, Opioids and Cancer Pain that we published in 2009 and then again, updated in I think 2010-2011. It actually got an award from the British Medical Association, as a book in oncology. But I worked with Paul Glare, Janet Hardy and we did the book twice but he sent me off in interest in that and part of that interest was looking at the basic pharmacology and the initial chapters that were done were through Gav. So, I invited him to do that because I knew what a consummate researcher and what a pioneer he was, and he said yes. But I had to write it. So he would then help edit it and things like that.

Dr. Lynn McPherson:

Mm-hmm (affirmative).

Dr. Mellar Davis:

So he was really a very good mentor in that sense, you got into his mind and he was able to talk to you and then we invited him to speak and we spent time together and then we went to Japan to teach together but he became more of a... Not only a mentor but also a friend. A deeply respected friend, but he was very humble and despite his roots and all the things that he had discovered, so he became a

mentor at a distance so to speak. And we actually did a publication in 2019 just before his death actually, on the buprenorphine, which had been an interest.

It became an interest in 2005 when I did my first publication on it, I thought this was a very interesting drug and we did a series of other publications, like 12 reasons why you would use buprenorphine and one of the interesting things about this and I'll always remember this is that, Perry Fine came up to me and after presenting one of these things at the HPM or presenting it at some lecture and he said Mel don't you think that it should be a first line drug in hospice, because of its safety, so that was kind of an interesting thing with it. And we actually have a paper that's going to be published on the pragmatic use of buprenorphine that will be in current treatment options in oncology that will be coming out probably in the next several months.

So that's been a personal interest with it but I think the other thing that's really been confirming that, that's an opioid that we really should consider is the department of health and human services 2019 guidelines suggested considering this buprenorphine prior to using potent opioids. So I think that there's this evolving thing of looking at opioids in regards to safety, not only about efficacy. So I think we're going to be seeing this kind of evolving thing particularly in light of the opioid epidemic.

Dr. Lynn McPherson:

Mm (affirmative). So the fact that you did not respond to my email last week saying you and I should write a paper on how to convert off of buprenorphine is that more reflective of you're very busy or you think everybody and their mother should be on buprenorphine?

Dr. Mellar Davis:

No I think you're right I just haven't been able to respond to you. But I think the paper that's in current treatment options in oncology will come out with that actually.

Dr. Lynn McPherson:

Okay, good.

Dr. Mellar Davis:

At least some help in that regard. There aren't a lot of papers that have moved from buprenorphine into other opioids.

Dr. Lynn McPherson:

Right. I think that medical practice today is not comfortable with the idea of buprenorphine for pain management. Certainly for substance abuse recovery. But people don't quite know what to do with it and I think insurance companies are not familiar with that idea either. Connie you're certainly as a prescriber, I know when we get a patient in hospice on buprenorphine, the first question is how do I get them off of this.

Dr. Mellar Davis:

You know it's the same thing we faced in the early 2000's when methadone was coming back as an analgesic, you've got a lot of pushback, you've got a lot of pushback. But I think you just have to stay the course, the evidence is what the evidence is.

Dr. Lynn McPherson:

Mm-hmm (affirmative).

Dr. Mellar Davis:

You know that it is a good analgesic, you know I don't think that there's the perfect analgesic and maybe that will evolve with some of the basic science that is now looking at six transmembrane receptor agonists for opioids. So there may be this evolving theme that will be occurring but I think it's a drug that people should really consider because it is a safe drug. It allows you leeway that you don't have with other potent opioids. And the craving is less, so it blocks craving, so there is a safety mechanism with it.

Dr. Lynn McPherson:

But people are afraid of the affinity issue, and I can never remember should I not add bupe to morphine or should I not add morphine to bupe. So I think we've got some work still to do there.

Dr. Mellar Davis:

Yeah I think in low doses, for instance low doses of buprenorphine, there's actually synergy with hydromorphone morphine and what I'm talking are things like Belbuca or...

Dr. Lynn McPherson:

Butrans.

Dr. Mellar Davis:

Butrans or things like that. Once you get up to 12 or 16 mg probably when you get to 16 it's really difficult to get a response, analgesic response and so you end up having to divide doses or coming down on the buprenorphine to be able to get your potent opioid, if you're dealing with acute pain such as in the perioperative setting.

Dr. Lynn McPherson:

Mm-hmm (affirmative). Okay. Connie before I take a breath and plow on further, anything you want to hop in with yet?

Connie Dolan:

I mean no, I think this is just, so this is such a learning experience for our students to kind of think about this evolution of the science from the get go about medications and I think just this evolution still that science keeps emerging and how do we bring everybody up? Because I was listening to the buprenorphine right and it's this interesting part about when something's new and you don't have a pharmacist in your side pocket, like having Lynn with you all the time, how do you feel comfortable writing this because if you're at a community hospital where I am, you're supposed to be the expert. So how do we use this expertise to move it forward?

And then the second part I would say is again when you're at a community hospital and you have pharmacists who you kind of say, "Could you look at the literature?" And they'll look at their literature but not at the palliative care literature, and then you really have a hard time because the discussion can go places but then when you go into the community, so it's just interesting about what the science is and then how does it get spread out?

And then the comfort level and I think the other part with buprenorphine that I would just say even as a prescriber is this whole I don't want to say confusion, but there's been this guidelines of you needed to have this education and get a waiver and then during COVID they're not and then just being clear, okay what are the guidelines? Who is supposed to be prescribing it? Yes it's a really great [inaudible 00:19:35] in palliative care but how do we get that knowledge out?

So I think you've just articulated a lot of that.

Dr. Lynn McPherson:

Connie, nice. Go ahead.

Dr. Mellar Davis:

I think one of the probably most important things that I have learned over the decades that I've been in palliative medicine is that you bring things from the outside in. So bring the basic science. The basic science helps you and then secondly patients, when your back is against the wall, you become creative and if you have a knowledge of the basic science, in other words the things that Gav had brought forward, have really clinical utility that may be really very helpful in changing the field. Bringing it about, bringing new changes to the field, important changes to the field.

So I think, yes we need to read within the field, but if you read within the field you never bring anything new into the field. You need to read things outside of the field, you need to read literature that doesn't have a direct bearing on palliative care and often times we get locked into reading our own literature and then we don't really grow.

Dr. Lynn McPherson:

Mm-hmm (affirmative).

So Connie and I had the opportunity to speak briefly with Dr. Robert Twycross this morning and I started off by showing him, this is the first book that I ever bought in palliative care, his book. And my observation in talking to him and now talking to you, is we've come a long way from his smaller book called Oral Morphine is a Good Thing, to now we're talking about buprenorphine. Crazy, huh?

So here's my thought, people accuse me of not sleeping. But you know what I think I'm a slacker compared to you. You are absolutely, you are pumping out, you'll email me one day with something saying, "You know somebody ought to write a letter on this." And I'm like, "Yeah, somebody ought to." And then you write it the next day with 47 references and then the next day it's accepted and then the next day it's available online. That happened last week where you crushed my dreams by publishing that methadone may not be the NMDA receptive antagonist we think it is, especially at low doses. Talk to me about that. I'll play quietly while you discuss it.

Dr. Mellar Davis:

As I talked about bringing the basic science literature into the everyday practice. So when a basic scientist says that methadone has a high affinity for the NMDA receptor, he's talking about micromolar, now not very many people know about how do I convert micromolar into nanograms per milliliter and does that really get you the receptor site. That's really a good question. So for instance one micromolar of methadone is about 309 nanograms per milliliter of methadone. Now trying to get that kind of serum level in someone you're going to put them to sleep basically. You may be able to reach that in patients on high doses of maintenance methadone over a period of time, but you're talking about [inaudible 00:23:17] levels of 160 mg of methadone a day to be able to bind, get enough methadone into the CNS

to bind where that receptor is. At the same time hidden in the literature with methadone is that it's exquisite reuptake inhibitor of serotonin at sub-nanogram levels. That's seen in multiple animal studies, basic science studies, and you know you can get those kinds of levels into the brain.

And what we found in reviewing the literature, this is basic science and clinical work, is that actually methadone is like tramadol, it's not an NMDA inhibitor, it's a serotonin reuptake inhibitor and that's why you get the serotonin syndrome with it, multiple case reports of it, but it may be why it works in neuropathic pain, it has nothing to do with NMDA.

Dr. Lynn McPherson:

Now you're just talking dirty comparing my girl methadone with tramadol. That's just plain wrong. So what is the equivalent potency of methadone as a serotonin reuptake inhibitor relative to tramadol or to amitriptyline for example.

Dr. Mellar Davis:

It's close, it's close. I haven't looked at them directly, there is one paper by who is it, I'm not recalling right now, who actually did in animal models, looked at tramadol, levorphanol and methadone and found that they actually have the same affinities, except for the new receptor obviously tramadol was really very, very weak.

Dr. Lynn McPherson:

Okay.

Dr. Mellar Davis:

But I think that, that makes all the sense in the world with it so that was what the paper was about. The most recent thing is we're doing the update on managing bowel obstruction for inpatients with malignancies and we're looking at the pharmacological management and as you know there's one trial by Dave Pearl and company from Australia that looked at ranitidine and everyone got ranitidine and they got steroids and antiemetics and then they randomized people to octreotide and placebo. But everyone was on ranitidine, well I went back to look at the basic science literature in the 90's and early 2000's and ranitidine increases somatostatin levels by releasing it from the gastric mucosa. So when you give ranitidine and it's unique you don't see it with famotidine, so when you give ranitidine you're actually giving somatostatin to someone.

So the reason why that trial didn't show a benefit to octreotide is they were already giving octreotide when they were giving ranitidine. So it's one of the reasons why that trials negative we've never been able to explain that.

Dr. Lynn McPherson:

So that trial with Dr. Curo was IV ranitidine which we do not have here.

Dr. Mellar Davis:

You don't.

Dr. Lynn McPherson:

Would you expect the same with oral ranitidine here?

Dr. Mellar Davis:

You know that's an interesting question and I don't know if I can answer that, certainly if it gets to the gastric mucosa, it will increase the somatostatin levels, it does it through calcitonin gene related peptide. It releases that and that causes an increase in somatostatin levels and that's been seen both in humans and in animals, so it's not just an isolated study. There are about five or six studies that have demonstrated that ranitidine, uniquely not famotidine, not cimetidine, increases somatostatin levels.

Now what does that mean though in hospice? So if someone's on octreotide and they're able to take things in, maybe you can put them on high-dose ranitidine, oral ranitidine, like 400 mg twice daily, and they can go home and you will maintain the octreotide increase. And I've done that. So I've stopped the octreotide and sent them home on ranitidine.

Dr. Lynn McPherson:

So how would you investigate that? Is it a simple matter of the vial availability of ranitidine or do you have to look at serum levels or peak levels, or area out of the curve, or is it looking at a gastric mucosa tissue level?

Dr. Mellar Davis:

It may be a gastric mucosa tissue level, that's what my sense is, is that ranitidine causes calcitonin gene related peptide to increase and then somatostatin comes out. So it may be that oral will work, the reason that they gave it as a subcutaneous continuous infusion was people had nausea and vomiting.

Dr. Lynn McPherson:

Mm-hmm (affirmative).

Dr. Mellar Davis:

So if you're able to get it under control, maybe you can stop the octreotide and put them on oral ranitidine and send them on their way. [crosstalk00:28:47] Wouldn't that be neat? But that's bringing the basic science into potential therapeutic approach in something that's very pragmatic. Because hospice's can't afford octreotide but they can afford ranitidine.

Dr. Lynn McPherson:

Absolutely. So I know how I can make you cry like a little girl within 15 seconds. If I say, "This patient with dementia has delirium, let's give him haldol." Look there he goes Connie. So what's the dealio there?

Dr. Mellar Davis:

You know I don't use haldol anymore for delirium, I only use it for nausea. I really believe the Yager study, I personally believe it, now one randomized trial does not make a summer. And a negative randomized trial should be repeated, now the difficulty in repeating it is people with haloperidol actually have reduced survival. So people are going to be reluctant to repeat a negative study. At the same time when you look at all the systematic reviews of haloperidol and delirium, they're negative, all of the recent ones are negative. There's a preponderance of evidence that it's an ineffective agent in treating delirium. So I buy the data, I don't use it. So we've been using valproate, now the evidence for valproate is still observational studies so there isn't a randomized trial, looking at it versus placebo. I still think you could do a placebo trial based upon the Yager trial, because you had higher placebo responses than you

did with the haloperidol, so I think it needs to be subject to a randomized trial, but I don't use it anymore for delirium.

Dr. Lynn McPherson:

Mm (affirmative). It's caused quite a stir, I do know that for sure.

Connie Dolan:

Let me just ask one thing, Lynn, and I think the challenge as you both know so from the clinician perspective is, so delirium as long as I have been in practice has been a challenge, I can remember in the days when we were in the hospice part, we were giving everybody Thorazine which probably just zonked them. So then we sort of started to develop this, I think one of the challenges is delirium makes us feel helpless right? There is something that we can't figure it out or it is something in the disease process that we're not going to be able to fix. I think the other part that causes consternation is that as you both know, what you can do in an academic medical center sometimes has more flexibility.

What I really worry about Lynn, is what you talked about, when we're in the long-term care setting and we're trying to take care of these geriatric patients who may have a little bit of dementia underlying or not, they are already so restrictive in the medicines that we can use because even in my own experience, trying to get my mother on an antidepressant, they felt like it was chemical restraint. That was the attitude. So how do we help think and support clinicians, hospice and palliative across settings, because where I really worry about it and I think particularly with COVID is these long-term care facilities that don't have the support, they don't have a Lynn McPherson pharmacist in their back pocket who can help them think through, and so then the patient is left in this horrible state, the staff is terrified and it's just a bad outcome.

Dr. Lynn McPherson:

Yeah, it's a conundrum, it really is. So one last pharmacology conversation. Talk to me about P.E.A. What the heck's that?

Dr. Mellar Davis:

Palmitoylethanolamide is a nutraceutical, medicinal nutraceutical that's available. You can get it on Amazon. It is an ethanolamide but it's not an arachidonic ethanolamide. In hence, it doesn't directly bind to the classical cannabinoid receptors. It's a PPAR alpha agent. It works on the capsaicin type of receptor or the channel and it also may affect 5HT1A and the GPR55. Now that's all gargon so to speak but it's those kind of receptors have a lot to do with pain and modulation of pain. So the unique thing about these agents is they're modulatory, they are promiscuous in the sense of affecting multiple channels or so but they are also modulators of... It's like valproate is more of a modulator than attacking a single receptor, it modulates levels that occur in that. But it's a very safe agent, it's something that you normally produce when you have pain, it increases in inflammation, so in people with inflammatory disorders it will be increased in those particular tissues.

It works in neuropathic pain, there have been multiple, multiple studies in fact two meta-analysis that have been published that have shown that it actually works quite well in pain, in varied pain syndrome such as entrapment neuropathies, chemotherapy induced neuropathies, though there are no randomized trials in that setting.

And it has an antidepressant effect because it modulates a neuro inflammation, so it's actually worked in Parkinson's disease and there is a large interest among basic science researchers in looking at

it in Alzheimer's disease, so it's an agent that I think has a lot of promise and the really nice thing about palmitoylethanolamide is it has no side effects. It has less side effects than placebo. So it's a low risk agent to use, we use it in people with neuropathic pain, so we have several people with chemotherapy induced neuropathies who really have responded nicely to that without having the side effects for instance of duloxetine or gabapentin or things like that.

I have a woman who's had a postmastectomy pain pretty severe, she says that it's a god sent to her, it's really controlled her postmastectomy pain, so it's a nice adjuvant to use. In randomized trials interestingly enough recently published within the last year or two, it's worked in osteoarthritis. So in people that you're afraid of giving them an NSAID for whatever reason, bleeding or renal function, it's actually an agent that one could consider and it's synergistic with Tylenol, it's synergistic with some of the adjuvants, it's synergistic with several opioids, as an adjuvant. So either as a single agent or an adjuvant it's a good drug to use.

Dr. Lynn McPherson:

If you were to do one clinical trial in patients with an advanced illness, what indication would you evaluate it for?

Dr. Mellar Davis:

Me?

Dr. Lynn McPherson:

Yeah.

Dr. Mellar Davis:

I would target neuropathic pain. That would be I think, the low lying fruit.

Dr. Lynn McPherson:

Mm-hmm (affirmative).

Dr. Mellar Davis:

We don't have very many good agents for it and I would look it as a single agent or as an add-on. So adding it on to duloxetine for instance in chemotherapy induced neuropathy, would be a really interesting trial.

Dr. Lynn McPherson:

Why not head to head with duloxetine?

Dr. Mellar Davis:

What?

Dr. Lynn McPherson:

You could do it head to head, against duloxetine.

Dr. Mellar Davis:

You could. You could do several trials, or as an add-on and a failure. Or someone with duloxetine not responding to a randomized placebo, versus PEA study. So I think pain is probably the thing that I would target.

Dr. Lynn McPherson:

Mm-hmm (affirmative). So what dose would you use or start out our titrate to for neuropathic pain?

Dr. Mellar Davis:

It varies. We don't know if it does response relationship and trials have been between 300 and 1200 mg. I start at 800 and then I'll go up to 1200 with it. It's really relatively inexpensive, it's about \$20 or so a month. \$20 or \$30 a month.

Dr. Lynn McPherson:

Mm-hmm (affirmative).

Dr. Mellar Davis:

So it's a nice agent to use.

Dr. Lynn McPherson:

Yeah, I think we should put it in public water, what do you think?

Dr. Mellar Davis:

Yeah.

Dr. Lynn McPherson:

Yeah.

Dr. Mellar Davis:

You know it would be interesting to look at it from other kind of symptoms that are orphan-like. For instance, dementia, delirium, you know if it has a reduction in neuro-inflammation maybe it will modulate delirium.

Dr. Lynn McPherson:

Mm-hmm (affirmative).

Dr. Mellar Davis:

Now there's no reason why you couldn't really look at it, at least as an exploratory trial in that sense. [crosstalk00:38:36] Alzheimer's in animal models so, and it has worked as an antidepressant, so I think the other area that is rich for research is all those CNS disorders, whether they're inflammatory degenerative, such as Parkinson's disease, would be worth looking at.

Dr. Lynn McPherson:

Yeah. So we should hurry up and buy our supply from Amazon now, before Big Pharma gets ahold of this and we can't afford it anymore, right?

Dr. Mellar Davis:

You never know.

Dr. Lynn McPherson:

That's true. Connie, I think what you've seen here is an example of looking ahead in palliative care with research and all of the things that Dr. Davis has been involved in. What are your thoughts on that? What are the implications for our students?

Connie Dolan:

Well I think for our students, again thinking about palliative care and I think Dr. Davis you kind of really focused in on some of this research on pharmacology, which we didn't really know about in general and sort of thinking about how to focus on it and yet you've also spoken to thinking about what are some of the things that are going on in other types of care, other conditions that we can bring in, because otherwise we're just kind of re-filtering what we have, so I think being curious again about the data, paying attention to what's going on in the larger scheme of things.

I think the other part is sort of thinking about the language, as I listened to you and Lynn, you're talking a different kind of pharmacology language that some people may or may not be comfortable with but I think we have to gain some knowledge in how to evaluate some of the studies and how to interpret them. Because I think the one thing that we didn't kind of hit upon is that by the nature of the population that we serve in hospice and palliative care, we usually don't have large randomized samples and the follow-up for some of these patients may be really short, right? So we usually have very small sample sizes and they might be regional, and so I wonder also if there's some thoughts about that just in terms of what it means to do good palliative care studies?

Dr. Mellar Davis:

Yeah, that's a very good question. I think randomized trials are still there but the population in palliative medicine is certainly heterogeneous and that adds an element of not really knowing. You may target a population but it's a very broad population. And obviously there's a short survival, so safety definitions in palliative medicines are going to be different than for instance in other drug trials that will do phase four studies, long-term studies to see long-term safety. We don't have long-term generally in our population. So it's the acute safety that we're interested in. I still think that randomized trials are really important as far as evidence. Observational studies I think can complement that, I think to neglect observational studies for randomized trials alone is to miss perhaps a subset of patients that actually may respond, that you may have missed in the randomized trials. But to accept observational studies alone to the neglect of randomized trials is really poor science.

So we may have only observational studies and that's the evidence that we have and we act on that evidence but we hope to be able to expand that evidence to also look at randomized trials. And yes, small randomized trials can have errors in them and more often err on the positive than the negative side in that regard but one of the things about small randomized trials is if you could repeat small randomized trials and come up with the same thing, then that's actually much stronger than a P value of a single trial. The effect size of a single trial will be overwhelmed if it can be repeated by multiple groups and get the same result. It is likely that the effect size will get smaller by repeating the study, but if you get the same results by repeating it, it's much better than significance.

So it may be that you have multiple centers of palliative care that are, as you said we can't do the large cardiovascular studies, or the large studies but we could do small randomized trials and if

we're able to repeat them, in other words, coordinated system of repeating those kind of studies, then I think we'll be further ahead.

Dr. Lynn McPherson:

Absolutely. Absolutely. Certainly a PhD is a research degree Dr. Davis, but I could see a lot of the students you graduate with this degree maybe not performing the research, but I see a big role for them interpreting the research. Would you agree?

Dr. Mellar Davis:

Yeah I think so. I think that's a real big issue with it is looking at a study, looking at it's strengths, looking at obviously it's weaknesses and biases that are there and being able to interpret that, that's actually very important for any physician reading the literature. It's not just reading the bottom line, but looking at how they got to the bottom line that's really the important part of a study.

Dr. Lynn McPherson:

Absolutely. So in addition to the things that we've already mentioned, any other advice to our students as they graduate and move on their career?

Dr. Mellar Davis:

Read each day at least an hour. I was told when I started into medicine that I should read four articles for each patient I see, which I couldn't do, but I try to read on patients that I see still clinically and I learn something every time I'm on a clinical rotation. I learned something dramatically new because patients are the best teachers. So if you listen to patients, they'll tell you what's working and what isn't working. If you listen closely you'll know whether it's working or not working.

Dr. Lynn McPherson:

Mm-hmm (affirmative). Well if they just read one of your papers everyday for the rest of their career, that should last them a good 40-50 years, don't you think?

Connie anything last from you?

Connie Dolan:

No I just thank you for sharing this interesting part because I think people coming in may think that all of this was sort of established over the last decade and they don't understand that the science and research into the medications has been going on for 60 years and what we were working with and I think it's just so interesting to think about some of the challenges of research, of thinking about medications, thinking about Lynn, you were joking about access, but what happens with some of these medications as patents wear out and we're trying to think about cost containment and then the last part of with our science and we have to justify it to insurance companies to get them paid for and the level that you're talking at Dr. Davis sometimes, we're getting somebody who's doing a prior off who has no knowledge for us even to talk to. So it's just kind of interesting about how do we have to both read, interpret and then be able to communicate.

Dr. Mellar Davis:

Yeah.

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Dr. Lynn McPherson:

We're still trying to convince people that IV to oral hydromorphone is not 5:1, based on 1987 data, right Dr. Davis?

Dr. Mellar Davis:

That's right.

Dr. Lynn McPherson:

That's right. Well thank you so much, I really enjoyed this, my life is so much richer because of you and I really, really appreciate you, so thank you so much.

Dr. Mellar Davis:

Uh-huh (affirmative).

I'd like to thank our guest today and Connie Dolan for the continuing journey in our podcast series titled, Founders, Leaders and Futurists in Palliative Care. I'd also like to thank you for listening to the Palliative Care Chat Podcast. This is Dr. Lynn McPherson and this cut presentation is copyright 2021 University of Maryland. For more information on our completely online Masters of Science PhD and Graduate Certificate program in Palliative Care, or for permission requests regarding this podcast, please visit graduate.umaryland.edu/palliative Thank you.