

Palliative Care Chat – Episode 21 – Interview with Dr. Kathryn Walker and Dr. Meller Davis

“Magical, Mystical, Mischievous Methadone – Let’s Learn How to Use Methadone Safely and Appropriately”

- 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 because I have two guests today and they're both very good [inaudible 00:00:18].
- Dr. McPherson: The first is Dr. Kathryn Walker who is Senior Clinical and Scientific Director for palliative care with MedStar Health, and an associate professor at the University of Maryland School of Pharmacy. And Dr. Mellar Davis who is Director of Palliative Services with Geisinger Health Systems. Welcome both Dr. Walker and Dr. Davis. How are you today?
- Dr. Davis: Thank you.
- Dr. Walker: I'm well.
- Dr. McPherson: Yeah, we're very excited. So we are here today to talk about my favorite drug in the universe, it's such a favorite of mine that in Baltimore, where I work they call it McMethadone. So Dr. Davis, why is methadone an awesome choice for us to talk about?
- Dr. Davis: Well, it's an inexpensive drug, it's long-acting, it can be effective when other opioids are not effective. It has multiple routes of administration that can be used. So it can be a great go-to drug. Usually used as second line but has been reported to be used in first line.
- Dr. McPherson: Mm-hmm (affirmative). Yeah, I think increasingly. I know I'm seeing it being used more first line in hospice. Kat, why don't you explain what we did, we're a troop of naughty kittens, what did we do and why did we do it? And of course, this whole thing is leading to sharing with our listeners our fabulous publication that published in the Journal of Pain and Symptom Management on the safe and effective use of methadone. So why don't you clue in our readers on the background.
- Dr. Walker: Yeah, and how did we get here? How did this publication come to be after all of the different versions of consensus building that it took? Aside from our shared passion for using methadone, many of them trained by you, and no brainwashing, just training.
- Dr. McPherson: Of course not.

Dr. Walker: Well in 2014, I think we were all informed by the American Pain Society in collaboration with College on Problems of Drug Dependence and Heart Rhythm Society, and when they collaborated and brought forth these guidelines of best practices for methadone safety and efficacy. I think it informed a lot of decision making around methadone and how to use it safely. But all of us practicing in pain and palliative care and hospice, especially when you're treating patients where long-term survival for our patients changes the goals of care that we have, we were all kind of thinking, "Well, how does this apply to our patients? And how ought we take these guidelines and extrapolate them to the patients that we care about?" That guideline was focused on populations with much longer survival. So, the risk-benefit looked a lot different than the patients that we're usually struggling with making decisions over appropriate use.

Dr. Walker: In patients where the goals of care have shifted, they really need rapid pain relief in a lot of times and then you wonder how aggressively should we be monitoring these patients? So we were really striving to find the evidence-base behind it and where there was a lack of evidence-base, some consensus building of experts that have a lot of experience using methadone to say, "Where there's not strong evidence, here is best practice from what we know." We spent a whole day of 15 interprofessional hospice and palliative care experts to kind of really go over the existing data. There were physicians, pharmacists, there was a nurse, to really weigh in on making sure that it was appropriate for several different practice settings. There were some very spicy conversations around that.

Dr. Davis: Sure.

Dr. McPherson: [crosstalk 00:03:53] yeah, really spicy.

Dr. Walker: Which led to how long it took to really come to consensus on a lot of these things in the paper. I think we're all thrilled to think that we actually got there.

Dr. McPherson: Yeah.

Dr. Walker: For much of what you'll hear us talk about today and what you'll read in the paper.

Dr. McPherson: I remember a couple times during the meeting, Dr. Davis was sitting next to me, me leaning over to him and muttering, "Fix this for me." People were coming to [inaudible 00:04:18] us I think.

Dr. Walker: Yes, yes.

Dr. McPherson: I think one pretty cool thing right out of the gate is that our table one in the paper, which is patient selection for methadone. I'm going to talk very briefly about who I think is a good candidate. Well, maybe I'm not the best person in the world because I think they'd have to be like dead before I'd say maybe

they're not. But I think if we look at the things that kind of rose to the top are people with moderate to severe pain, and as Dr. Davis said, particularly as a second line opioid choice.

Dr. McPherson: I think the big one for me is their first line regimen just was not getting the job done. Also, even though it's exquisitely rare, somebody who has a true, finantering morphine allergy, methadone is sufficiently dissimilar that it might be a good choice. I think we all look at methadone or fentanyl for people with significant renal impairment because we have largely inactive metabolites from our friend, methadone. One thing I really like, as Dr. Davis already said, it's a long-acting opioid, but inherently, not because it's been pharmaceutically altered.

Dr. McPherson: I know in hospice patients, even if they're completely obtunded we can use the methadone 10mg/mL oral solution and put a small amount in the buccal cavity, prop their upper body up about 30 degrees so they won't aspirate, and it's a beautiful thing. Methadone is a very salifiable drug, so you do get a substantially more transmucosal absorption than you would with morphine. But I don't even really care about that because it just kind of really, really slowly trickles down their throat. Sometimes we're using a tenth of an mL, half of an mL, often. Very low doses. I think also, methadone's a good choice for people with high opioid tolerance or having side effects from other opioids. And again, because of the [inaudible 00:05:54] dysphasia, difficulty swallowing, are people who have a feeding tube.

Dr. McPherson: So Dr. Davis, fair balance here kills me, but who might be a potentially inappropriate candidate for methadone?

Dr. Davis: Well I think it's someone who's older, living alone, that you're worried about them taking their medications, poor cognitive function, without really a responsible caregiver. I think someone with a history of abuse of drug, this is a drug that can have a high fatality rate if misused. So you'd need someone who's really reliable. Someone with a substantial substance of use, particularly if they're using poly substances. You can get into trouble with this. Multiple risk factors I think are important and looking at patients. People for instance with transplants, who may be on immunosuppressive drugs that may influence the pharmacology or on multiple other drugs that may in fact prolong the effect of methadone. Patients with prolonged QTc intervals, since this drug can produce arrhythmias, may not be candidates for this. And individuals who have significant organ dysfunction, not so much kidney failure, but liver failure, may have it in advanced stages of prolongation of the half-life of the drug.

Dr. Davis: The other is, I found in people who have rapidly changing cognitive function near the end of life in which they can't really participate in scoring their pain severity. That might not be an individual that you want to have on methadone. In clinical practice, I found that people who, for instance, are undergoing blocks or having single fraction radiation, who may in fact respond rapidly, if you're

using methadone in that group of patients and they have a rapid response to non-pharmacological approaches, you may end up getting into trouble with some opioid side effects or respiratory depression if you've been building a dose of methadone.

Dr. McPherson: Mm-hmm (affirmative), okay. That's quite a laundry list. I know my good friend, Dr. Doug [Orlace 00:08:28] in Canada, is always saying, "Buprenorphine can take a joke, but methadone has no sense of humor." So I think we have very little wiggle room with these patients who may, in fact, be borderline. So Dr. Walker, before we get into specific comorbid conditions that could alter our decisions to use methadone or not, can you give us a picture of what we recommended as a general overview of the risk assessment before starting methadone?

Dr. Walker: Well I think we started out by all endorsing that it is so important to do a risk assessment, as it is with every opioid. I think you'll see that thought process played out in table two. This table kind of highlights the risk assessment and things that apply to all opioids, including methadone. We felt it was important to put that column in there because there's some risk assessment that you should be doing with every opioid. Some of the things that Dr. Davis talked about, liver function, you want to think about that with every opioid. But we didn't want people to forget that methadone's an opioid. So you got to think about that with methadone too.

Dr. Walker: We also added in things that were specific to methadone that is kind of over and above the traditional risk assessment you would do for opioids. That were things like structural heart disease, and electrolyte abnormalities. Those were things that you know, you don't always think about hypokalemia when you dose a regular opioid. Those are things to just highlight what people add on. So, those paper talks a lot about individualizing it, which we're very good at doing in palliative care. Everything's individualized, right? That's important, and we've already talked about the cognitive status for our patient. As always, history, and targeted history and physical exam.

Dr. Walker: As a pharmacist, I would be remiss in not mentioning medication reconciliation because in our view, as a pharmacist, that is such a crucial part, especially with methadone. We're going to keep you in suspense here because we're going to talk about drug interactions in a few minutes.

Dr. Davis: That's right.

Dr. Walker: That's a big part of it.

Dr. McPherson: But I'm not giving you three weeks to have that conversation.

Dr. Walker: I get that.

Dr. McPherson: We certainly could use all that time. So Dr. Davis, why don't you talk briefly, if you could please, about the history of liver disease in a patient where we're thinking about methadone therapy?

Dr. Davis: Yeah. Methadone has a metabolite that really is not considered active, though there is some controversy in the literature about that. It's relatively safe in mild to moderate liver disease, but it's metabolized by type-1 mixed-function oxidase enzymes, particularly CYP3A4 and 2B6, and maybe a little 2D6. In patients with advanced liver disease, those enzymes may be reduced and you'll actually get a fairly long effect of your methadone. So in treating people with liver disease, I think it's obvious starting low, going slow and you may want to reconsider this drug, particularly if they have a Pugh Class C liver disease. This may not be one that you'll want to choose.

Dr. McPherson: Okay. Good advice. Well, Dr. Walker, I know we didn't spend a whole lot of time on it, but what do you think about people who do have a history of substance use disorder?

Dr. Walker: Yeah, good point. I mean, this is not the focus or really within the scope of the paper. The two main things I think we came to terms with is including it just for completeness sake was ideally best practice would be that patients are co-managed by an addiction specialist. But I don't know about everyone else's world but wow, that's hard to do in palliative care. They're hard to fine. But if you have one, absolutely that's the best way to go.

Dr. Walker: But then we also really wrestled with this, especially in your end-of-life population, about what to do with patients who are using illicit substances. We recommended in this paper that we found we all came to terms that that was a contraindication. So there was a little note in there about our professional obligation to treat pain. But we wrestled mightily with this, in what to do with those patients that still are actively using. But it's really hard with such a drug with a risk like methadone, to know where you stand if someone is using something illicit on the side. That was a recommendation we put forward in the paper related to that.

Dr. McPherson: Exactly, exactly.

Dr. Walker: [crosstalk 00:12:52]

Dr. Davis: I think-

Dr. Walker: Sorry, go ahead.

Dr. Davis: I think it's important too, if you're looking at urine toxicologies that methadone isn't really in the standard dipstick toxicology. So if you're going to really do urine studies in patients who may have a better prognosis, you're really going to

have to order the methadone in particular. It won't be in the standard screening.

Dr. McPherson: That's a good point. Thank you.

Dr. Walker: Yeah, great.

Dr. McPherson: So I think if I woke up one day and I did not get an email from some listener that deals with drug therapy about yet another drug that prolongs the QTc, I would probably think that the apocalypse had arrived. Dr. Davis, talk to me about patients with a history of cardiovascular disease, and then perhaps spend a couple of minutes on the whole QTc issue. What is the dealio?

Dr. Davis: Okay. Well, methadone inhibits repolarization by inhibiting the potassium channel expression that occurs on ... And as a result, what happens is you get reentry arrhythmias in what is called torsades de pointes, which is a pretty refractory ventricular tachycardia that is managed by magnesium but can be highly fatal. The QTc monitoring is recommended certainly by the APS and people who have prolonged QTc intervals should probably not be considered for methadone. Now, there's a correlation of QTc prolongation with the risk of torsades. So in patients who have corrected QTc intervals, so 450-500, you have a moderate risk. Over 500, most people say you probably shouldn't be using methadone. Or if they do have that prolongation of the QTc interval on methadone, you ought to reconsider changing them to another drug. There is an assumption though, and there is a gap in the knowledge about risks, QTc intervals in methadone and that particular relationship. A lot of this is expert opinion, but I think it's an important safety factor in people who do have a good prognosis.

Dr. Davis: The difficulty I have with methadone and in patients who are, for instance, on amiodarone, who have very prolonged QTc intervals, it's hard to know whether it's safe to start it or not, and I generally haven't used it in those patients. Now, does amiodarone protect people from torsades, is a real question. There is no data to suggest that. On the other hand, if methadone is the only drug you have, then it's talking about risk-benefits with patients. I had one patient who had a head and neck cancer. When she was on third line methadone, probably the only drug that we had left, and her QTc was prolonged, I sat down and talked with her and said, "You know, this is what we're dealing with. I don't really have another option, but you're at risk for sudden death." She basically said to me, "Well, it's a win-win then." So some people are willing to accept the risks for the benefits of methadone. But it's really important to talk to patients about risks and to tell them why you're getting QTc intervals if you are in the palliative setting, I mean.

Dr. McPherson: Mm-hmm (affirmative). So you know, you hear this total daily dose thrown around. Like, "Oh, if somebody's on methadone less than 30mg/ day, it's

extremely rare." Do you buy that? That it's really a dose-related effect and if they're on 30mg or less than that a day, it's probably a very, very low risk?

Dr. Davis: There are people with silent QTc prolongation syndromes, inherited syndromes. They may actually be more sensitive to that. I don't think you can buy that. Certainly there is a dose relationship to QTc prolongation, but you can actually even see it at lower doses.

Dr. McPherson: Okay. What about heart failure patients? Can we use methadone in those folks?

Dr. Davis: They are at increased risk. So that, I think again they probably should be monitored. If people have diastolic or systolic heart failure, I think they really need probably to be monitored because their risk is higher. Now why they are at increased risk for QTc interval's not really well clarified in the literature, and most of that is by epidemiological data. But the answer is yes.

Dr. McPherson: Okay. You mentioned in the paper that individuals with heart failure have a greater incidence of sleep-disordered breathing. So, what are your thoughts on that? Whether it is stemming from heart failure, but there are a lot of people who have disordered breathing. Should we use methadone or avoid it in these patients?

Dr. Davis: Well there are ... it's kind of a triangle. Because people with heart failure actually have increased sleep-disordered breathing, and increased sleep-disordered breathing increases the sensitivity to opioids. Certainly methadone has correlated significantly with sleep-disordered breathing. So, in certain studies, as many as 30% and one study as high as 75% of those patients had sleep-disordered breathing or increased apnea-hypopneic index. Now what happens in these individuals is they are actually increased sensitivity to hypopnea or apnea at night. So during the day, they may look at you and not seem to be influenced at all from their breathing rates or so. But during sleep, there's an increased dependence on hypoxic drive.

Dr. Davis: What happens is, during apnea and during the hypopneic episodes, there is a hypoxia that occurs. It leads to arrhythmia. So many of these patients may actually have arrhythmias at night and not ... infrequently, the deaths from methadone will occur at night rather than during the day. So in someone with sleep-disordered breathing, this is probably not a drug I would use. Now, the methadone will produce both obstructive and central sleep apnea. You could say, "Well, let's just throw them on a continuous BiPAP or a continuous positive pressure airway breathing." The positive pressure airway breathing can help with obstructive sleep apnea but won't really help in central sleep apnea. We don't know whether that will prevent opioid deaths by doing that. So will I feel safe if someone's on CPAP with COPD and sleep-disordered breathing and using methadone? Probably not. I would still feel a little uncomfortable doing that.

Dr. McPherson: Mm-hmm (affirmative). So you might feel better, but the patient may not, huh?

Dr. Davis: Yeah.

Dr. McPherson: I've often heard that monitoring for worsening snoring is certainly a valid parameter to monitor for methadone toxicity. But I've also heard you don't get snoring as a warning shot with central sleep apnea, is that true?]

Dr. Davis: That's true. That's really the difficulty in that. Opioids produce a complex sleep-disordered breathing, so you get both. You can, in the same patient, get obstructive and central sleep apnea.

Dr. McPherson: Mm-hmm (affirmative). Great. Well, based on everything Dr. Davis and Dr. Walker just said, we did have in this article, table three, which is recommendations for ECG monitoring and action steps. We took an interesting approach. We broke the entire patient population in hospice and palliative care into three groups.

Dr. McPherson: So we said we would have a high level of vigilance for both baseline and followup ECG monitoring. For those patients whose goal of care was curative, life prolonging therapy, full steam ahead, it just happens that palliative care is in the loop in providing some guidance. For those patients, particularly when methadone is used as a first line opioid, we pretty much recommended going with the American Pain Society recommendations in 2014. Getting a baseline EKG if they have positive risk factors, which include things such as what was mentioned, hypokalemia, hypomagnesemia, impaired liver function, structural heart disease, including congenital heart defects, history of endocarditis or heart failure, and genetic predisposition from patients in families with QT syndrome. Also, anybody who had a prior QTc of 450 or higher, or a history suggestive of prior ventricular arrhythmia. And then we have a whole laundry list of consider a baseline EKG with no additional risk factors, QTc less than 450, and then our recommendations which are very consistent with what Dr. Davis just said. Think twice before 450 and 499, and probably don't go there at 500 or higher.

Dr. McPherson: Then we have our moderate level of vigilance, which are people who are going for the curative life-prolonging therapy but perhaps methadone is a second line opioid because the first line options didn't really work out. Or a patient who's more on the hospice boat, where we're pretty much just going for the comfort measures, or perhaps just palliative care is in charge, and potentially using it in that scenario as a first line opioid. Where we would instead discuss the risks and benefits with the patient and the family, in light of the goals of care. Routine baseline ECG monitoring not really recommended, but might consider it depending on the patient's baseline risk status and their wishes and their goals of care. If the decision is made not to get a baseline ECG, I would document it. But if you do obtain one, follow the recommendations as shown with the high risk group.

Dr. McPherson: And then the last is the low level of vigilance, which are patients clearly who are just in it for comfort measures. We would not recommend an ECG unless there really was a compelling indication, but if you chose to go in that direction to follow the recommendations as above. So I think that should be very helpful to people to figure out what's the best way to handle this.

Dr. McPherson: So skipping to a different content just a little bit, Dr. Walker, talk to me about the 80,000 googabazillion drug interactions with methadone.

Dr. Walker: Okay, so how long do I have?

Dr. McPherson: You've got 30 seconds. Go girl.

Dr. Walker: We could stay here all day long because there's so many. Which is why it makes the job of a palliative care pharmacist so much fun. So basically, let's break it down into two things. The paper, we really were hoping that this would be a good resource and you'll find some really good resources. There's a table here that's available online. It's not part of the printing because it's so long, it's like a scroll. But we basically focused on kind of describing the issues with drug interactions globally and then really giving the readers the evidence-base for what you see for the specific drugs that are commonly interacting with methadone.

Dr. Walker: So if you look at the ones that are opioid receptor mediated adverse effects, and then non-opioid receptor mediated adverse effects. When you look at ones that are associated with the opioid receptor, you're thinking of sedation, respiratory [inaudible 00:25:08]. When you're looking at the non-opioid receptor mediated adverse effects, that's where you see QTc prolongation, torsades, sudden cardiac death. Basically when drug interactions cause an additive pharmacodynamic effect, that's when you think of things like when you add in a benzo with using methadone. Which is like a big no-no, right? Because you're going to add ... it is not a good look to have this increased risk of sedation, sleep-disordered breathing. So you'll see through there, there's a big focus on medications for their QTc interval prolongation.

Dr. Walker: The most commonly reported medications went to the FDA database were HIV meds, benzos, there was ceftriaxone, trimethoprim, some antibiotics. That was about 42% of the common drug interactions. We included a reference for QTc interval table. Some of the major enzymes that Dr. Davis covered already were the 2B6, 2C19, 3A4 and 2D6. I like kind of the other pieces in here, I think that would help especially when you're looking for primary palliative care people to be thinking about this, are just some pearls in there. Like, for instance, non-medication related interactions, like cigarette smoking. Which I think sometimes we don't always ask about. But that can induce 2B6, and it's [inaudible 00:26:32] because that's primarily responsible for methadone levels and clearance. So I think that's something that even when someone stops smoking, it can come to

normal levels and then calls it normal. So even if someone stops smoking, you're like, "Hooray," then that might change your methadone level.

Dr. Walker: So essentially, the main two recommendations we made from this section aside from giving an awesome table for reference, I hope people will use it, is that when you start out medications that impact methadone levels, you really need to do a full assessment. When you start medications that have additive clinical effects, such as being a sedative, affecting breathing and QT intervals, both of those should require getting out your magnifying glass and really going through the med list carefully. So I think that's my kind of explanation. How'd I do? Did I [crosstalk 00:27:22]

Dr. McPherson: Well you went way over your 30 seconds but it was good stuff. So I agree. I think people forget to reconsider what's the scoop when you stop medications and someone continues on methadone. I'm always talking about my little tip of when I'm on the phone and I'm driving around the beltway and doing my nails and eating a donut and somebody calls me for a methadone recommendation, I ask about the three A's. Because I'm really concerned about drugs that will inhibit the metabolism of methadone. So I ask about amiodarone, antidepressants, and anti-infectives. If I get a no to all three, then I know that's covered a good chunk of the serious offenders. But if I get a yes, then we have to drill down a little more deeply.

Dr. McPherson: It's interesting when we consider things like fluconazole for thrush. We do know that 80% of the time if someone has thrush, one dose of fluconazole 150 or 200 will kick it. It may take four days to see the clinical improvement, but it's a strong 3A4 inhibitor, and if someone's on methadone, if they're just taking one dose, I don't fool with it. But if the prescriber's going to put them on fluconazole for a week, and the patient was really, really comfortable on their methadone, I may in fact, empirically reduce their dose by about 25-30% just to be safe. I think that's so important.

Dr. McPherson: Well I think what everybody's been waiting for with breathless excitement is the dosing recommendation. So Kat, why don't you talk to us about the interesting approach that we took to opioid naïve patients, because you know we are rebels and we do, in our hearts, love methadone first line.

Dr. Walker: We kind of do. Although, I'll say we did this with a little bit of a soft hand here because of how we roll and being pretty cautious, but also, I think you'll see, using methadone in opioid naïve patients is controversial.

Dr. McPherson: It is?

Dr. Walker: So I think one of the things we put right out there is this is not garden variety methadone dosing, you put it in the hands of experienced practitioners. The European Association for Palliative Care recommends that methadone may be

used as step three opioid. In some of these circumstances, they were like, "Okay. At least there's someone out there who's still with us."

Dr. Davis: We're moving to Germany.

Dr. Walker: I mean, APS, when they say opioid naïve patients shouldn't exceed 7.5 a day, so that's like 2.5 three times a day. There's some data, like Salpeter demonstrating that you can use low dose methadone. I think that's where we went with it, was to say we recommended for our group that you could go 2-7.5 and it allows for that very low dose methadone. Because we know that you can sometimes give patients a 1mg by mouth, even once a day sometimes. But we put the low dosing 1mg twice a day and that they should not ... we both agree. So that's a little bit of a difference from what they recommended.

Dr. Walker: We accounted for amounts to go a little bit lower in the dose for an opioid naïve patient, which is important in our population because of the second point, where we both agreed, so the APS guidelines and our guidelines would agree that they should not be escalated quickly. This is no more than 5mg a day and over a long period of time to allow for steady-state, because in our population, it takes so much longer. Methadone has a steady-state of 5-130 hours, but in our patients it can be even longer than that. So that really ... start low, go slow applies here for sure. I think we allowed a little more leniency than the APS guidelines in that area.

Dr. McPherson: And like Dr. Davis was talking about, liver disease, it could take two weeks to get to steady-state. Would you agree Dr. Davis?

Dr. Davis: Yep.

Dr. Walker: Yep, absolutely.

Dr. Davis: So yeah, I think with organ function that you'll probably be even slower in titrating.

Dr. McPherson: Mm-hmm (affirmative).

Dr. Walker: Yeah. So our guidance is 5-7 days but yeah, with that you could wait two weeks before you can-

Dr. McPherson: Rely on your breakthrough. Another thing I liked that we did, that was consistent with APS is we took people who are on up to 60mg in oral morphine equivalent, and we threw those in the opioid naïve bucket, which I thought was really interesting. So it's kind of half way between opioid naïve and opioid tolerant patients. Those low-dosers, we kept those in the opioid naïve dosing bucket. And then when we look at opioid tolerant patients, so what we're referring to here is people getting greater than 60mg a day of oral morphine equivalent, we said if they're between 60 and 199mg of oral morphine

equivalent, and the patient was less than 65 years old, we would do a 10 to 1 conversion. Every 10mg of oral morphine equivalent would be 1mg of oral methadone. If they were on 200mg of oral morphine equivalent or higher per day and/or over 65 years old, we'd be recommending a 20 to 1 conversion.

Dr. McPherson: Now granted, the first thing somebody will say is, "That's not evidence-based yet." Yes, I know. But remember, this guideline is to give practitioners in hospice and palliative care a harbor of safety where we can reach an effective dose as quickly as possible but not harm the patient. Dr. Davis, do you want to elaborate on that? Because this was a big deal for us.

Dr. Davis: Yeah. I think that this is a drug that could produce pain relief fairly quickly. The thing that I really worry about is if someone gets analgesy with the first dose, you're really-

Dr. McPherson: You're in big trouble. [crosstalk 00:32:40]

Dr. Davis: Yeah, the patient may be dancing but I have great fears. So, I think this needs close monitoring in that sense. Starting low, going slow is really very important with this drug.

Dr. McPherson: Absolutely. Perhaps you could keep on going and talk to us a little bit about methadone as an adjuvant analgesic. I know often we will use this strategy when a hospice patient is very close to the end of the road, but they're kind of a red hot mess. What are your thoughts on that?

Dr. Davis: Yeah. Well, the original work on this, the non-cross tolerance, and the fact that methadone may add to morphine, for instance, came from [Bon 00:33:21] and Pasternak in 2002, where in mice models they found that by adding methadone to morphine, they had synergy that occurred. It wasn't related to the NMDA receptor. It was probably because methadone binds to different types of mu subtype receptors than morphine does. So there have been several papers that have added low doses of methadone to morphine in patients who are not responding well to morphine, and have demonstrated responses in about half of those patients. It is one of the things that has recently occurred, I think over the last four to five years, is now using methadone as an adjuvant.

Dr. McPherson: Mm-hmm (affirmative). What kind of dose would you start in somebody who maybe had 3 to 5 days left to live? Would you continue their current opioid regimen or just sprinkle a little methadone on top?

Dr. Davis: Yeah. I think that what I would do is start with 2.5 a couple times a day, three times a day. I actually have a woman in the hospital, just to take a point of view, who is dying from her rectal cancer, and she's on hydromorphone as a continuous infusion and was on oxycodone, not able to swallow. She was on 80mg of oxycodone twice a day. So what I did was switched her to methadone 5mg three times a day and continued her hydromorphone. I think it's certainly

related to opioid dose they're on, but I think starting, again, low. Some people have used as low as 2-4mg twice daily as an adjuvant. We have evidence that it probably is effective in a subgroup of patients, we don't have a lot of information about what dose to start with. Again, I think starting low is probably the thing to do.

Dr. McPherson: And I suspect it's probably, when it is efficacious, thanks to the mechanism of action of being an NMDA receptor antagonist. Do you concur?

Dr. Davis: I think that's part of it. I think part of it too is it plays differently on mu receptors, and different subtypes. It's like playing the organ, you get an octave and you get multiple chords that you can play in the pain.

Dr. McPherson: There you go.

Dr. Davis: As far as pain is concerned. So I think that that's part of how it works too.

Dr. McPherson: Yeah. And if I could just pause and give a shout-out to your dear friend Dr. Pasternak who just passed away. I'm sure he is in heaven right now arguing with God about 25 different flavors of mu receptors. So, very appreciative of his life's work there.

Dr. Davis: Oh yes.

Dr. McPherson: I'd like to ... very much so. I'd like to spend just a moment on alternate routes of administration for methadone. Certainly methadone comes as a 5, 10 and 40mg tablet, although the 40 is reserved for methadone clinics. It does come in three concentrations of oral solutions. In hospice, we routinely use the 10mg/mL because we can use it as an intense [inaudible 00:36:48] in the buccal cavity, as I shared earlier. Also, pharmacists, God loves them, the ones who compound. It's too much like cooking for this girl. They can make rectal suppositories, and the dosing would be 1 to 1 with oral methadone. And of course, we have parenteral methadone formulations. We have a preservative-free, and one with the preservative.

Dr. McPherson: So because methadone is about 70-80% bioavailable, even though it is that highly bioavailable, I should say, we do still recommend cutting your total daily dose in half when you move to the IV route of administration. However, when you're going from IV to PO, I would not multiply by 2 because of the high bioavailability, and there's great variability I may add, we recommend multiplying your total IV daily dose by 1.3 when you reestablish going to the oral. Just to point out that the preservative formulation, it's the corbutanol really increases the risk of QT prolongation, all by itself, that naughty kitten. And of course, you would use the preservative-free if you really wanted to explore non-axial use of methadone, which is way beyond the scope of our paper. So Dr. Walker, we've beaten this to death. What do you think about monitoring?

Dr. Walker: Well that is a big part of what we were talking about in this paper. When we went through with the group and said, "So, what are we going to do?" We went through the level of vigilance, and I think you talked a little bit about how to monitor per EKG. We also talked about caregiver monitoring, I don't know if you want to talk about that at this point, but that was a big part of our patient education section as well.

Dr. McPherson: You know what, I think you and I, with you being primarily an inpatient palliative care practitioner, me being the hospice girl, we have had many conversations about it's really difficult for you and your team to start methadone, or Dr. Davis in his practice, and send them out the door day two. Because as Dr. Davis said, you do not want to be a rockstar on day two, because if you do that, on day five you're going to jail. How does your team handle that when you want to start methadone but you really don't want to keep them in the hospital five days?

Dr. Walker: Yeah. That's hard because sometimes you don't know can we commit to five days or not, are we sure? So yeah, it's hard unless you have someone that is trustworthy taking [inaudible 00:38:54] that you feel like will be able to continue the plan of care, it is a very large challenge. Typically, we look for hospice partnerships when we're looking for a hospital to hospice transfer. There are not as many partners in the community that are comfortable taking a hand off for a methadone dosing and titrating. We offer to be available to consult, but I think the challenge is if they are going to a hospice scenario, then you are more comfortable if they have a protocol in place to do that and you can talk a little bit more about what that looks like to make them feel comfortable. But if they're not, and they're going home and their PCP's like, "Yeah. I'll see them in a week."

Dr. McPherson: Oh no.

Dr. Walker: You're like, "Well, that's not good enough." You really need every day during this getting to steady-state period. But then you would need, the only cases we really feel comfortable doing that is, is a very, very savvy caregiver that we can talk to. So we'll talk a little bit about that in the patient education section. But you really want to be convinced that someone is laying [inaudible 00:39:55], knowing what to look for and knowing for signs of when that steady-state hits what is going on with the methadone. If they're able to call [crosstalk 00:40:03]

Dr. Davis: We've been very fortunate having a nurse navigator in our outpatient area. So we could start someone in the house, give the education, and then have our nurse navigator make those calls on a daily basis if they're not going to hospice.

Dr. McPherson: You are fortunate.

Dr. Davis: Yeah. So having a nurse navigator who's very savvy about methadone and can check up on the family and see how things are going. It adds a safety net to the use of this or when you're changing from one service to another.

Dr. McPherson: Absolutely.

Dr. Walker: Yeah, absolutely.

Dr. McPherson: So, what would you ...

Dr. Davis: I think the other issue, and Kat may want to address this, is methadone on a palliative unit and methadone on a non-palliative unit. When I was at the Cleveland Clinic, we didn't like using methadone in-house unless we had nurses that were pretty savvy about giving it and could recognize toxicities in it. We felt much more comfortable actually giving it on the unit, which actually gave us the ability to use different dosing strategies. So Kat, I don't know how you guys handle that in the inpatient unit.

Dr. Walker: Yeah, no, that's a good question. We actually only have two hospitals with hospice units, or hospice beds, but we don't have a palliative unit. So I'm jealous of you for that because I agree. Using it on the regular hospital unit, we are very careful about who's going to be getting the nurses up to speed, but then you know when shift change happens, who's going to come on the next shift, you never know. It is a little bit of a challenge. That's why we're fairly hesitant to do it on the inpatient side as well.

Dr. Walker: Another thing we've realized too is that some of our hospitals don't have different dosage formulations of methadone available. That's been a little bit of a challenge. As far as the nurse's comfort level though, in this area, since we practice in Baltimore, our nurses have seen a lot of methadone. So they're not worried about it, but it's more of that they see so much of it, that they're not worried about it. So we're usually having to bring it to their attention like, "Okay. This is not your normal substance use disorder methadone once a day treatment. This is ... We need to actually pay attention to this." So you're absolutely right. I think in the hospital floor we're pretty cautious about that as well.

Dr. McPherson: Definitely. What we've set up in hospice is when we start a patient on methadone, we have a requirement that the hospice nurse visits the patient every day for the first five days. We have an actual suggested monitoring protocol that we use. So for example, certainly looking at therapeutic effectiveness, assessing the pain. We'll talk about education next, but an important part of the education is explaining to the patient that methadone is like climbing the stairs of a staircase. It's going to take you four to five to six days to get to the top of the staircase, so you do have to use your breakthrough medication. Which is a real challenge sometimes in a facility where we often know that PRN stands for patient receives nothing. That's another whole conversation.

Dr. McPherson: But the nurse certainly will explore therapeutic effectiveness. So pain severity ratings and the ability to perform their activities of daily living, and looking at

potential toxicity. So if respiration is slowed or irregular, apnea. We do ask about snoring. Altered mental status or vision changes, looking at their eyes, looking at their pupils. We use a sedation rating scale. Then all the other traditional opioid adverse effects such as confusion and nausea. We'll always ask that they track any changes in their medication regimen, as Kat was just describing, because of the drug interactions. Their ability to swallow.

Dr. McPherson: And then I think another really important thing is our nurse will spend a lot of time educating the caregiver in the home. One thing we tell them is, every two hours during waking hours, we want you to stop what you're doing and go lay eyeballs on the patient. Are they becoming increasingly sleepier? Is it harder and harder to wake them up? If you don't see methadone toxicity coming, it's because you are not looking. We really partner with the family to get this done. We do also have an exception that is if a patient is in an excellent caregiving situation, the nurse can maybe skip one or two of those five days if they can call and speak to that reliable caregiver, professional or a lay person, and go through the laundry list. So Kat, what else do you want to add about patient education and family education?

Dr. Walker: Well, I think of the topic that we wrestled with the most in this section, within our group, was naloxone. You can see it's carefully worded in here, which we went through several different iterations of how strongly or not strongly to word this, but I think the main point to how we came to consensus on this is that it makes sense to have an action plan and that that action plan is individualized. That may include naloxone, but I think what a lot of people were worried about, rightfully so, is that patients that are actively dying look sometimes very similar to patients that are having an overdose or the situation as they're getting into steady-state or other reasons. So changing in breathing, confusion, sedation, like, "Wow. That looks a lot like," and you would not want someone giving naloxone to an actively dying patient. That's not a good way to leave this earth, is in withdrawing from opioid use when you're hopefully controlled with pain.

Dr. Walker: I think we talked about having a written and oral communication plan, having an active plan saying, "These are what to look at. Here's what to do if you see it, who to call. Holding the dose until you are able to talk with someone, and what to monitor for." I think we added it in there with that kind of caveat around it. Because I think we know of a lot of health systems, and regions, and states, that are kind of have that, "Give patients naloxone." In our health system it automatically prints out along with any opioid order. So it was something we felt like was important to address.

Dr. Davis: Yeah.

Dr. McPherson: [crosstalk 00:46:14]

Dr. Davis: I think the other thing is to look at the respiratory pattern. So chain smoking is not an opioid-induced breathing disorder, but people will have some periods of apnea, then they increase their breathing rate and then diminish it. So they have his waxing and waning breathing pattern. That's not an opioid-related breathing pattern. You need to really instruct families that that's really part of the dying process and not related to the methadone. If you see quantal breathing, where people are skipping an inspiratory beat, so to speak, just like a Mobitz II heart block, that may in fact be an opioid-induced breathing pattern. We use breathing patterns to help as far as education of families and adjusting opioid doses.

Dr. McPherson: That brings up an excellent point, Dr. Davis. Because in the state of California, they had passed a law that anyone who's on an opioid above a certain amount, which is pretty darn low, or perhaps also on a benzo, automatically has to have a prescription for Narcan. And they did not do a carve out for hospice. I frequently get a call from a hospice nurse saying, "I'm sitting here looking at the patient, and I'm not sure if he is fixing to die or if he is opioid overdose, and I'm very reluctant to give the next dose." If we have skilled nurses who struggle with this, we're really up [inaudible 00:47:45] creek if we're giving this nasal Narcan to a family member saying, "If they look like they're opioid overdose, go ahead and slam them with a full dose of Narcan," and then we're really going to be in a pickle, aren't we?

Dr. Davis: Yeah.

Dr. Walker: Well and you wonder, are they familiar with checking for pinpoint pupils, and is there other education going on around that, not just the breathing.

Dr. Davis: Yeah. So the pattern's helpful but the other problem obvious with Narcan is it's half-life is a half hour and methadone's is hours. You'll get a response to Narcan if it is related to methadone, but then they'll go back into their respiratory depression. It may be, and we've had to in the inpatient ward when I was at Cleveland, occasionally have to give a continuous infusion of Narcan in patients who had respiratory problems with methadone. It's not a one shot does it and you can give it and forget it. You've got to come back and monitor that patient.

Dr. McPherson: And I think it's difficult for families to do.

Dr. Walker: Absolutely.

Dr. McPherson: So that makes me very concerned. Kat, any last patient education points or advice you'd like to stress?

Dr. Walker: Yeah. I think that was an important one. The only other one that I think we thought was important to address that doesn't always get played into other guidelines because our patients are, a lot of them nearing death, is the importance of disposal. Anyone with an opioid should be counseling patients

and ... giving opioids should be counseling families on safe storage. So that, I think is kind of a best practice across the board. But in our populations we often do have to talk about disposal. You have disposal when you change doses but then also after a patient dies. So I think that's something that we mention in here as far as take back program, flushing down the toilet, mixing with impallable substances. I think that's something to keep in mind if you're developing patient and caregiver education on any opioids, but especially methadone.

Dr. McPherson: Very good.

Dr. Walker: Because the danger in sharing it, or having that passed on is much greater than you would think with other opioids.

Dr. McPherson: I always say, "You don't store your money on the kitchen table. Don't keep your medicine there either." Of course we all know what happens when a visitor says, "Can I use your restroom?" They're checking out your medicine cabinet.

Dr. McPherson: So Dr. Davis, any last comments from you as we wrap up?

Dr. Davis: No. This has been great.

Dr. McPherson: It has been great. I'd like to thank Dr. Davis and Dr. Walker for their awesome assistance in recording this podcast. So the paper again is titled 'Safe and Appropriate Use of Methadone in Hospice and Palliative Care: Expert Consensus White Paper.' I'd like to thank the authors; Doctors Walker and Davis of course, Dr. Eduardo Bruera, Akhila Reddy, Judy Paice, Kasey Malotte, Kshelle Lockman, Charles Wellman, Shelley Salpeter, Nina Bembem, James Ray, Bernard Lapointe from Canada, and Dr. Roger Chou. Boy, that reads like a list of rockstars, don't you think?

Dr. Walker: Honored to be part of the group.

Dr. McPherson: Absolutely. It's the Journal of Pain and Symptom Management, and will be published hard copy in March of this year. But I will put on our website the link that's good for a few more weeks to get the full text article free. Thank you again to my guests. Again, this is Dr. Lynn McPherson and this presentation is copyright 2019, University of Maryland. For more information on our completely online Master of Science and Graduate certificate program in palliative care, or for permission requests regarding this podcast, or the link to get the full text article for the next few weeks, please visit [graduate.umaryland.edu/palliative](http://graduate.umaryland.edu/palliative). Thank you.

Speaker 1: Hello?