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'm delighted to have multiple guests today. I have Dr. Tanya Uritsky who's a Clinical Pharmacy Specialist in Pain Management and Palliative Care, Hospice of the University of Pennsylvania in Philadelphia. I have Dr. Rabia Atayee from the Department of Pharmacy, San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, La Jolla, California. And Dr. Chris Herndon from the Department of Pharmacy Practice of the School of Pharmacy, Southern Illinois University, Edwardsville, Illinois.

My three colleagues as well as a fourth colleague who could not join us are all co-authors on a paper published in the Journal of Palliative Medicine, titled "Ten Tips Palliative Care Pharmacists Want the Palliative Care Team to Know When Caring for Patients."

Dr. Uritsky, how did this come to be? You want to give us a little background?

Dr. Uritsky: Absolutely. So we all put our heads together and came up with the 10 things we really thought were important for anybody who's providing palliative care or hospice care to patients to know from a pharmacy perspective. We were kind of asked to do this in a real formal way, but we came up with these ideas, and we all agreed on what would be most important. And the truth is as a pharmacist, one of our important roles is to optimize symptom management for palliative care patients by providing evidence based and patient centered medication therapies. And also to ensuring the optimal use of these medications for symptom management in palliative care. And because pharmacists are critical members of the palliative care team but are not always as accessible to some palliative care teams more than others, we thought it would be great to provide some of what we know in a more formal way.

So that being said, I'm gonna jump into one of the tips for starting. So, the first tip I'm gonna discuss is Drug-Induced QTc Prolongation. Generally QTc prolongation is dose and route related, and so while it's uncommon at the doses that we typically use of medications in palliative care, it is associated with an increased risk of Torsades de Pointes, of which I'll from this point on call Torsades, and it can result in ventricular fibrillation and sudden cardiac death. So it's important we know about this and what the risk factors are with the medications that we're actually using quite commonly.

So we know in palliative care patients that at baseline they have a prolonged QTc in general. Usually it's not severe prolongation. So with Torsades, we typically think of that as an increased risk of a QTc over 500 ms or when there's a change of greater than 60 ms in that interval. So there is no known true threshold though where Torsades is likely to occur. There are some known predictors of QT prolongation and that does include things like QTc prolonging medications, hypokalemia, elevated serum creatinine, female gender, structural

heart disease, advanced age, and prolonged baseline QTc as well as bradycardia and drug interactions. So one thing that people may not be thinking about is the supplements or herbals that your patients may be taking. And so something like grapefruit juice can increase the risk of these types of drug interactions due to the inhibition of the cytochrome P450 system. It's always important to think about those other things people may be taking and ask about them.

When we think about medications that can potentially prolong the QTc, we always want to use the lowest effective dose and always reach for our oral administration route whenever possible. There is a dose dependent risk associated with certain medications, and that's been seen with tricyclic antidepressants, medications like chlorpromazine at higher doses of above 100mg, and even with ondansetron, and that's been about one or two hours after giving it via intravenous administration.

One medication we also commonly use is haloperidol, and we know that at lower doses of haloperidol the risk is not [inaudible 00:04:15] but at higher doses, but generally also in the literature we see that intravenous administration of Haloperidol has as much as a two-fold greater risk of QTc prolongation than when given in the oral route. And there is a significantly higher risk that's associated with doses of greater than 15mg/day. So sticking to the lower doses and when giving them orally can be better tolerated and safer.

So, we also know that QTc prolongation is rare with atypical antipsychotics, and there is virtually no QTc prolongation from aripiprazole. There was a study done that compared oral haloperidol and oral olanzapine as a four-fold increased risk of QTc prolongation with oral haloperidol. The dosing in this study was quite high, and was more for the antipsychotic dosing was 15mg of haloperidol and 20mg of olanzapine. So at the lower doses its risk is less significant. But I think it's important to note the difference between the two drugs.

So another drug that's commonly used is metoclopramide. And at the doses that we commonly use for motility disorders, they're not typically associated with QTc prolongation. Higher doses that used to be used at antiemetics for pre-chemotherapy are more likely to be associated with QTc prolongation. Other drugs that are generally not associated with QTc prolongation includes sertraline, paroxetine, and duloxetine.

When we are thinking about other antidepressants, mirtazapine and trazodone also have a low risk of QTc prolongation at therapeutic dosing. A common drug that comes to mind when we think about QTc prolongation is methadone. It's also what commonly comes to mind when we think about palliative care and hospice care. And so if you look at the studies of methadone and QTc prolongation, it is really more associated with those very high doses over 100mg a day. And other risk factors are present, including drugs that interact with methadone's metabolism.

In general, when using a medication that can increase the risk of Torsade de Pointes, or of QTc prolongation, we always want to be extra cautious, assess our risk factors, and then [inaudible 00:06:25] to the next, make a good decision on how to dose, again using the lowest dose and trying to reach for oral whenever possible.

So, the next tip I can offer up, would be on that of olanzapine. So, olanzapine has really become one of my favorite drugs more recently in that I found it just treats so many different symptoms. And so, there's growing evidence to support the clinical evidence in that it has shown to have benefit in treatment of nausea, as well as things like appetite and insomnia, may be helpful in those symptoms as well. There is a more generally large adverse effect profile and the cost may be prohibited, especially in hospice situations where your dollars are more limited.

So, olanzapine is an atypical antipsychotic, and it does have a very complex receptor binding profile. It has had an established role in the management of delirium, of fierce psychosis, and psychotic disorders, as well as severe mental health disorders. There is more and more data supporting its use in symptom management, specifically in nausea and vomiting. We know that nausea and vomiting generally leads to appetite and weight loss, can lead to mood level decreasing as well as overall just poor outcome. So, when we have symptom clusters like this, oftentimes we have patients on multiple different medications to target each different symptom. And the kind of beauty of Olanzapine is one agent you hit so many receptors that you treat a lot of this symptom cluster with one drug.

So, olanzapine combines dopamine, histamine, muscarinic, and serotonin receptors, and that's really what makes it very effective in nausea and vomiting. I'd kind of call it the kitchen sink of an antiemetic. It hits everything. So, based on it's receptor profile, studies have been that supported use of olanzapine for nausea and vomiting in oncology, and as a result, the American Society of Clinical Oncology has added olanzapine to its antiemetic regimen for their highly emetogenic chemotherapies, as well as for use for breakthrough nausea and vomiting.

There also is data demonstrating that palliative care patients can benefit from olanzapine for the treatment of nausea and vomiting as well. And as I previously stated, I've seen some very good benefits for patients who have refractory nausea and vomiting, and they really do a lot better when they started olanzapine.

So, this same receptor binding profile is actually what causes a lot of the potential side effects, and that's why people tend to reach for the drug a little bit later, because it does hit so many receptors, it can cause a lot more adverse effects than a drug that's more targeted. So, because of it's strong [inaudible 00:09:28] muscarinic, and the histaminergic receptor, olanzapine can be

sedating, we like to take advantage of this property and dose it at bedtime, and try to help people get some sleep if they're suffering from insomnia.

It also has these wide side effects that I talked about in all these different receptors that can likely lead to weight gain as well, which if people are nauseous and vomiting, they're generally not eating and so weight loss is common.

Finally, it can also help with depression and anxiety, as it has serotonin activity and dopamine activity, but it also has activity at the GABBA or the gamma aminobutyric acid receptor, like the benzodiazepine. So it can also help with anxiety and mood.

As previously mentioned, there are lots of side effects, and common immediate side effects include those anticholinergic side effects like dry mouth and constipation. Orthostasis can be a problem, especially for our older and more frail patients, and so we have to make sure that we are aware that this can happen, and it can increase the risk of falls. And there also may be dose-dependent extrapyramidal symptoms. Generally the dosing we're using is lower, and so we don't have as much of a significance issue with those, but it's important to monitor.

And so there are longer term effects as well, but those can include glucose changes, hyperprolactinemia, and alterations in liver enzymes. The issue with cost is that oral olanzapine is more expensive, significantly more expensive than oral haloperidol or chlorpromazine in it's orally disintegrating form, which may be reached for in someone who's not keeping things down as well, it's even more expensive. So, if we are reaching for olanzapine, it's important to think about using for it's multimodal properties and then discontinuing the other antiemetics that would be covering similar receptors.

Dr. McPherson: Dr. Uritsky, if I can jump in, I think that the cost is not only a barrier, last time I checked it was about $15 a tablet. I'm curious what the rest of you have experienced when a patient comes from the inpatient environment perhaps to home or to home-based hospice? We have a heck of a time using antipsychotics particularly in nursing homes and assisted living facilities, even when we're using it for nausea and not for behavioral disturbances. Anybody else have any experience with that, having a hard time?

Dr. Herndon: Well, I couldn't agree more. This is Chris, and what we typically find too is that a lot of our long-term care facilities in our area will give us tremendous push back, mostly due to their concerns around some of their quality metrics ratings, even though those metrics specifically state that they should not be applied to patients that are enrolled in hospice.

Dr. McPherson: Yeah, I think that's so important. And someone else was starting to say something?

Dr. Atayee: You know, I just wanted to add, even though I primarily work in the inpatient setting, we do get a lot of push back on it, and we have to schedule the antipsychotic use for nausea, but also provide a lot of education, and in the nursing administration put in the indication for nausea, or anxiety, or a mix of those two symptoms versus as an antipsychotic.

Dr. McPherson: It makes me crazy when I hear from my hospice nurses about long-term care facilities who have a sign in the window saying "We are an antipsychotic free facility." And they're so darn proud of it, and Chris is right. It's all because of those stars ratings. That makes me crazy. So, I refer to them as antidopaminergic agents instead of antipsychotics. I don't think I'm fooling anybody, but I feel better.

Dr. Uritsky: Yeah, I tell my patients, I always have to explain to them they are in a psychotic facility, because inevitably they go online and look it up. And they're like, "You think I'm crazy. And I'm just nauseous." And so I always make sure they understand, we're using it as antiemetic. But it does become a problem when they transfer out at times. I only really work inpatient, but I've heard stories for sure.

Dr. McPherson: And ZOFRAN doesn't fix everything. Ondansetron is good for post-op nausea and vomiting and chemo-induced nausea and vomiting, not everything from soup to nuts. Would you all agree?

Dr. Uritsky: Agreed.

Dr. McPherson: Okay. Rock on girl.

Dr. Uritsky: Alright, so I will take one more tip, and then I'm gonna pass this off to some of my colleagues. So I am gonna address tip number seven, which is the immunotherapy drugs. So these are new blockbuster drugs that are coming about every day with new indications. These are drugs ending in -mab or -ib, and they're oral oncology drugs that are not chemotherapy. But they do generally have some adverse effects that can be managed, but we have to be aware of some of the limitations, and also kind of what our options are in management, as well as the relevant drug interactions and trying to use these drugs safely and effectively.

So, the adverse effects of immunotherapy can occur at any point. Most commonly they occur in the first 8 to 12 weeks of therapy. The most common things you may hear about is skin related toxicities, rash, or pruritus. And so, these side effects of the immune checkpoint inhibitors, which include drugs like ipilimumab and pembrolizumab. If they're a lower grade or mild to moderate severity, grades one through three, the adverse effects can generally be managed with topicals, like emollients and steroids.

When they advance beyond that, they may require things like systemic steroids. GI toxicity includes commonly diarrhea and colitis, and it's more common with ipilimumab. Grades one and two, which are mild to moderate, can be managed with loperamide and with electrolytes. But when it persists, or when it advances beyond to grade three and grade four, usually it requires a break from immunotherapy treatments, and treatment with high doses of systemic corticosteroids.

If cases are refractory to these treatments, then they can use infliximab to try and get relief from the toxicity. Nivolumab and pembrolizumab most commonly cause an immune related arthritis, and this symptom can be palliated with the use of nonsteroidals or COX-2-selective inhibitors, or the use of non acetylated salicylates like choline magnesium trisalicylate or salsalate.

If symptoms are more moderate, it may require a low dose steroid, between 10mg and 20mg of prednisolone or equivalent, and higher doses if the symptom is more severe or progressive. The use of systemic corticosteroids is not an absolute contraindication to immunotherapy. There is data supporting using steroids, and saying they don't really affect the impact of immunotherapy. And then there is also conflicting data saying that maybe they do. And so, because of that, it's really important when thinking about using steroids in your patient who's receiving palliative care, that you first discuss this with the treating oncologist and ensure that they're okay with using steroids. If it's an emergency situation or severe adverse reaction, and you have to save a life, that makes sense. But if we're using it to treat other ailments, you may really want to think about ensuring that we get approval before initiating it in patients who are receiving immunotherapy.

Oral tyrosine kinase inhibitors, or TKIs, these are the drugs often ending in -ib, things like erlotinib, or sunitinib can cause skin-related toxicity, diarrhea, and can change hair pigmentation and also cause neuropathies. It's important that TKIs have an acidic environment to be absorbed. So, while the data on the outcomes for this interaction are limited, using proton pump inhibitors may actually decrease progression-free and overall survival when used commonly with sunitinib or erlotinib.

So, if we are using an H2-receptor antagonist or an oral antacid solution together with an oral TKI, then patients should take their H2-receptor antagonist, like ranitidine or famotidine at least two hours after their oral chemotherapy in order to minimize the risks of its interaction.

Just some important things to think about when you think about immunotherapy drugs and our palliative care patients.

Dr. McPherson: You know, those TKIs, aside from the side effects you talked about Tanya, they're actually fairly well tolerated, which becomes quite a conversation for us in hospice. Because you could consider them to be drugs that palliate the

disease process, so really they are the financial responsibility of the hospice. So, we have quite a few conversations about that.

Dr. Uritsky: I imagine that's challenging.

Dr. McPherson: Yeah, and I just had a question when I was in Montréal last week about using a steroid with one of the immunotherapy drugs. I mean if you have somebody with screaming metastatic bone pain, it's hard to say no to that, to using a steroid to treat that pain.

Dr. Uritsky: More and more of the providers I'm seeing are more amenable to using them given that the data is showing that there's likely less impact than we think. So, I think that's a good thing. But we still come up against, every now and then, someone who won't let us do it. And then it's hard to explain. What do you do? How do you manage this pain?

Dr. McPherson: There you go.

Dr. Atayee: And I think it does matter if you're using if for palliation of symptoms versus if you're aiming for more reduction in the disease or tumor load. So I think that's where I've seen more of the push back, is if they want more than just palliating the symptoms with the immunotherapy.

Dr. McPherson: Yeah, that makes sense.

Alrighty, who's next Tanya?

Dr. Uritsky: Who do we have next? We have Chris.

Dr. McPherson: Okay.

Dr. Herndon: Alright. Well, thanks for inviting me. I'm super excited to be here with all my palliative care compadre. And thanks for allowing me to work on this important project with all of you.

My tips are on the benzodiazepines and the NSAIDs. To start with on the benzodiazepines, what we typically find in our hospice program is that everybody gets a prescription for lorazepam, whether they need it or not. And I think that some of the important issues with benzodiazepines the palliative care team really need to know are, and these are not in any order of importance, but I think number one, the half-life when you look these drugs up in most of the pharmacy information resources, the half-life of these drugs do not always reflect the duration of action of these medicines. The medicines, for instance diazepam or even lorazepam, the actual anxiolytic benefit of those drugs may be significantly shorter than the actual reported half-life due to the redistribution within the body.

I think the second thing I'd like to share with the audience is to make sure, even though it's rare, that everybody has in the back of their mind the paradoxical reaction that can occur with benzodiazepines in which agitation versus anxiolysis is actually realized. I have to share a particular case that we had in a patient that was brought from the hospice into our institution and was put on a midazolam drip and titrated up and up and up, and the providers just could not figure out why we were not able to get this patient calm and comfortable. And it was something that slipped, I think, most of the folks minds in the heat of the moment. And I think it's really important that that gets kinda put somewhere on the top of the page when you're using these medications, especially in the hospice patient, that we don't forget about the potential for this paradoxical agitation.

The third thing that I think is very reasonable to talk about, and again coming back to at least our practice, is that a lot of people get put on these, I guess, admission orders, where we gotta make sure we have everything that the patient might potentially need in their home. And what we typically wind up seeing then is that lorazepam ... And I don't mean to pick on lorazepam. It just seems to be the most commonly used ... Gets used for a lot of indications that I think people take for granted. We see benzodiazepines and mainly lorazepam used quite frequently for the treatment of dyspnea in our palliative care patients.

However, there may be some question around the actual benefit of using benzodiazepines in the treatment of dyspnea when there's not an underlying anxiety component to that. I know that anxiety and dyspnea frequently play in the same sand box together and can be seen together. However, when we do have dyspnea without anxiety, I'm not really sure that the benzodiazepines may be the best choice. And we should potentially be leaning on those drugs that have a little bit better data, namely the opioids.

And the thing that we battle frequently with our hospice population is that the risk verses benefit of using opiates and benzodiazepines concurrently, especially when we're using them for the same indication.

I think lastly, one thing that I want to make sure those of us that are using benzodiazepines, especially in the long-term care facility world or palliative care, is that old, handy mnemonic lot or LOT. And that stands for lorazepam, oxazepam, and temazepam. And these reflect the benzodiazepines that do not undergo phase one metabolic reactions. And so theoretically may be a little bit safer in those patients that have hepatic compromise.

And I don't know, for those of you who've been around for a little while, you may recall when lorazepam was back ordered everywhere ... It's probably coming up on about 20 years ago ... And all of the hospices that I have had to work with in that period of time all had to quick spin themselves up on the use of oxazepam versus lorazepam.

I don't know. Do you remember that, Lynn?

Dr. McPherson: Uh, vaguely, yes. I'm only 29 though Chris. So ...

Dr. Herndon: Oh, that's right. Sorry.

Dr. McPherson: Hard pressed to remember 20 years ago.

Dr. Herndon: So, I guess in short, you know, benzodiazepines are incredibly helpful in our patient population, and they're really, I think, part of our essentials medicine list, even as we put boots on the ground. But I think that we really need to consider their use in more of a patient-centered approach and not in such a shot-gun pattern, that they're used today.

Dr. McPherson: Yeah. Chris, when you said a mnemonic you were gonna mention, I thought you were gonna say a ham sandwich, because it seems like so many hospice patients, "Boom. Welcome to Hospice. You get your Haldol, your Ativan, and your morphine, your ham sandwich."

Dr. Herndon: Yep.

Dr. McPherson: Yep. But you know we are kind of in a tough spot right now, because the opioids are naughty kittens, the opiates and the benzos are naughty kittens, the opioids and gabapentin is not a good look. I mean, what is left? Good Lord, what's left?

Dr. Herndon: Hugs.

Dr. McPherson: Yeah. We have a hug therapy for hospice. Great.

Dr. Herndon: Hug therapy.

Dr. McPherson: That'll fix it. Hug it out.

Dr. Herndon: And this is something that gets argued about frequently. And I don't have the right answers of when you should and should not use these. I think that we take the combinations of benzodiazepines and opioids for granted sometimes.

Dr. McPherson: Mm-hmm (affirmative)

Dr. Herndon: I don't know if most of our audience is familiar with this, but opioids by themselves are fairly effective anxiolytics on their own.

Dr. McPherson: Mm-hmm (affirmative)

Dr. Herndon: And so, it may require a little bit of second thought around how we're gonna tackle dyspnea and anxiety, especially when they're being treated simultaneously and occurring at the same time.

Dr. McPherson: Yeah. But I think that data about using benzos for dyspnea came from Navigante. And those patients had like one foot in the grave and the other on a banana peel. And they got them a [inaudible 00:25:47] infusion, but they were like literally hovering on the brink of death. And what I find interesting is the data from Dr. David Hui from MD Anderson, looking at using the benzos in a little bit of a higher dose for people with delirium. And it actually showed benefits. So, boy, I'm really confused now.

Dr. Herndon: Well, if it's okay, we'll move on to the next tip. And this was a tip on NSAIDs. And unfortunately I see, at least in our practice, NSAIDs overlooked quite a bit in the palliative care and hospice patient population. And despite having fairly effective analgesic benefits, both alone and in combination with opioids, a lot of times I think our providers will frequently believe that we've got the pain side covered with the opioid, and we don't need to add on an analgesic theoretically that's less potent.

NSAIDs come in numerous flavors, and I think that the right NSAID should always be targeted to the right patient. They can be invaluable for adjunctive therapy for bone pain. And the problem with this is that a lot of times I think the GI and renal adverse effects that typically we consider when we're going to initiate NSAIDs, I think spook a lot of our prescribers. And I agree that that should be something that's of concern. And obviously we want to make sure we're not initiating NSAID therapy in patient's with pre-existing chronic kidney disease that may come into our palliative care practices or patients who have heart failure with reduced ejection fraction.

I have to call on I guess my star pupil, and that's the nonacetylated salicylates. That tends to be our favorite go-to drug at the end of life. And the reason for this is they tend to be very, very poor COX-1 and COX-2 inhibitors. So if you compare their inhibitory concentration or IC50, compared to some of the other more commonly used NSAIDs that we may see, like naproxen or ibuprofen, I almost even question calling these drugs actual NSAIDs. The class of drugs I'm talking about includes salicylate, diflunisal, and choline magnesium trisalicylate.

And the thought behind this is, is that because they're so weak in inhibiting COX-1 and COX-2, that this probably is going to reduce side effect burden for patients, in terms again of renal, GI, and potentially most importantly bleeding risk. The data around this, to actually support it, I think is fairly sparse. And so it does kinda hamper our ability to really come out and forcefully and unequivocally state those, but I think that for people that have been in and around the palliative care world for quite some time, they'll tell you that they do tend to be, while weaker, better tolerated.

And we're still trying to figure out exactly how these drugs work. There appears that there may be a tumor necrosis factor-alpha inhibitory component. And it also looks like they may inhibit nuclear factor-kappa beta as well as some microglial nitrite secretion. So what all that actually means for our palliative care

patients, I think is left to be seen. But there are patients that respond to this and given the propensity for potentially lower adverse effects, they may need to be moved up in our essential medicines list.

The other thing I think is important to note for our palliative care folks is we shouldn't forget about our topical NSAID alternatives for superficial pain due to osteoarthritis and some of the other types of arthralgia and myalgia that our end-of-life care patients frequently experience that may not be directly related to the terminal prognosis. I do need to make sure everyone is aware that we don't use topical NSAIDs for bone pain. I have seen that order written in the past, and that's something that we need to make sure we're not doing. This is for superficial osteoarthritic conditions only.

So that sums up my two tips. Again, thank you for allowing me to participate in this.

What are some other folks doing in terms of NSAID therapy in this patient population?

Dr. McPherson: You know, I think one conversation we have often is picking between a steroid and a non-steroidal for somebody with metastatic bone pain. And I always think about do they have diabetes or major GI issues. And of course if they have major GI issues that kind of shoots both of those. But that's one thing we think of. And, frankly, I'd rather use the steroids than a non-steroidal.

What do you think Chris?

Dr. Herndon: I actually agree. A lot of it I guess would depend around what type of therapy they're already on in terms of where they're coming in from a chemotherapy standpoint. I get really nervous about using NSAIDs in patients who might have low platelet counts due to whatever type of treatment that they've already received. I also get really nervous about the propensity for GI bleed, like you were stating, but also for GI perforation.

You know, to my knowledge, I don't think corticosteroids, when used by themselves, at least in a healthy adult population, greatly increase the risk for GI bleed. It seems to be only when they are combined with other platelet activating agents, anti-coagulants or NSAIDs.

Dr. McPherson: Right. I agree.

Dr. Herndon: My favorite is dexamethasone for that indication. I think that for a lot of our hospice prescribers, what I tend to find with them is, is that they tend to want to sit on the corticosteroids for those types of indications too long. They wait too long to initiate because of their concerns around some of the corticosteroid side effects and HPA axis suppression.

Dr. McPherson: I agree. I agree. Well, you stole my thunder there Herndon, because I'm gonna talk about the steroids next.

Dr. Herndon: Sorry.

Dr. McPherson: My favorite line is, "Nobody should die without dex on board." So I'm with you on that one.

So I do think the corticosteroids also known as glucocorticoids or steroids, a very commonly used group of drugs. We use them for a bunch of things, such as pain, particularly metastatic bone pain, anorexia, cachexia, fatigue, nausea, vomiting, depression, brain meds, hypercalcemia, bowel obstructions, spinal cord compressions, superior vena cava syndrome ... I could just go on and on and on all day. And I do think there's no good data to support one over the other, although it does seem like we're all pretty much in love with dexamethasone. And I think this has to do with the greater glucocorticoid effect where 0.75mg of dexamethasone give you about the same kick as 5 of prednisone, but a far less mineralocorticoid or sodium in fluid retention of dexamethasone compared to the other steroids.

I think generally the dose that we see, typically I would say in hospice and palliative care, is 8mg a day. I just had a conversation today with a physician, because I generally recommend dex 4mg bid breakfast and lunch. And this physician was asking, "Why are you doing that? I thought it had a long tissue half-life?" Dexamethasone does have a very long tissue half-life of about 60 hours. So you could give it once a day, and maybe this is just an urban legend, but I break it up because of issues about the stomach. But Chris's point is well taken.

When you look at short-term therapy ... And I would throw in there, our median length of stay in hospice is 17 days. So a person who gets dex their entire hospice stay, we don't generally give GI prophylaxis. You don't even really need it. Chris's point is correct that we're only really worried about it when we combine it with a non-steroidal anti-inflammatory drug, which is not a good look by the way, because you increase the risk of bleeding by about 15 fold. So, I would just have them on a plain steroid. If I have to pick, I'm always gonna go with the steroid. And I would not worry about GI prophylaxis.

And again, I do love me a good incensol. Dex dose comes a 1mg/mL oral solution. You can put it in the buccal cavity, and that works out pretty well. So one of the acute adverse effects we have to worry about, thrush for example, edema, dyspepsia occasionally, very rarely GI alterations, certainly the glucose intolerance. Insomnia, that's why we say don't take it past 2:00 PM at the very latest in the day. And delirium and anxiety. So if it makes the patient a little crazy, and they want to jump out of the second story window and fly, you might want to move away from the steroid.

But even barring that, some prescribers feel like it's a moral, ethical, legal obligation to taper down off the steroid. I think that if the patient is responding and they're not having adverse effects and they're doing well, I say it's okay. You can go to heaven on dexamethasone. That works for me.

Of course there are longer term side effects, but you know, maybe if you're starting it in the palliative care arena before you even get to hospice, you may see some of these, such as the steroid facies, the moon-like facies, the fat redistribution, certainly the adrenal suppression, wound healing can be impaired, and so forth. But I do think that the steroids are a beautiful group of drugs. If you do decide to discontinue therapy, if they've been on it at least two weeks, I would probably taper down.

Any tips that I've missed, anybody?

Dr. Atayee: No, that was great. And I just wanted to add that our institution, our palliative care team does use it once a day without any GI prophylaxis. And we've seen no increase in any GI side effects. And we actually even did a study to see baseline if you have no delirium, if dexamethasone would increase your delirium, and we didn't notice any change in that. Now, obviously if you're starting point is delirium, we don't start someone on dexamethasone.

Dr. McPherson: Those are great tips. Thank you for that.

One other tip I would throw out that's not even in the article is our COPDers ... Oh, my gosh, all those bloody inhalers ... Often we will move somebody from all those inhalers ... Some of the dry powder inhalers in our patients who are at end-of-life, they don't have the steam to suck up the drug. So we will switch them duo-neb around the clock, every four hours while awake. You can even do albuterol q2 prn in between, and we will take the inhaled steroid and just go to dexamethasone oral, because it hits so many other indications that are appropriate in our population.

So I think we all have voted that the steroids are awesome, awesome drugs.

Alright, my next tip is about fentanyl, which I think is a pretty amazing opioid. But it's often used inappropriately. We do know that all fentanyl formulations, except the injectable, require the patient be opioid tolerant, which is defined by the FDA, as a patient taking 60mg or oral morphine a day or more for at least a week. So this is true of transdermal fentanyl and the six transmucosal immediate-release fentanyl formulations that are on the market. And those puppies you have to go through the REMS strategy, and they are very, very expensive.

So, transdermal fentanyl, again same thing, it's indicated for severe pain requiring daily, around-the-clock chronic opioids. I think there is some considerations before you jump in with transdermal fentanyl. If somebody is

very thin and wasted and cachectic, it seems like we don't get the same bang for the buck that we would expect for somebody with a normal body habitus. Certainly anybody with a fever ... I think a fever of 103 or 104 will increase the absorption of fentanyl by about 30 to 40 percent, so that can be clinically significant in my opinion.

I do know that people get a little confused about how to switch to transdermal fentanyl. If you look at the innovator product Duragesic's package labeling, they say if the patient is on 60mg to 134mg of oral morphine per day, to switch to the 25mcg/hour patch. But they even say in their own labeling, "This is very conservative." So, Breitbart popularized the method of you take the total daily dose of oral morphine in mg/day, you cut it in half, and that's your mcg/hour transdermal fentanyl patch. Dr. Reddy from MD Anderson found that it's closer to 40 percent than 50 percent, so between 40 and 50 percent.

I do also want to point out that we always think of the patch as available in five strengths, 12, 25, 50, 75, and 100mcg/hr. The 12mcg/hr patch you have to scratch your head and say, "What the heck? What's with that?" That is kinda misleading because you feel like, "Okay. If it's a doubling, should someone taking 25mg of oral morphine a day be allowed to start on the transdermal fentanyl 12mcg/hr patch?" And the answer is, "No". That 12mcg/hr patch is on the market for combining with other patch strengths. And I'll bet most of you did not know the transdermal fentanyl is also available as a 37.5, 62.5, and 87.5mcg/hr patch. So it's really just representing using the 12 with a 25, a 50, or a 75mcg/hr patch. So, I frankly never recommend using that 12mcg/hr patch. I don't even drill down that sufficiently to go there.

I do think the timing is important. When you apply a patch, it's gonna take about 17-18 hours, probably up to 24 to get it to pseudo-steady state. And it does take about three days to get to absolute-steady state. And we always think of fentanyl as a quick on, quick off drug. And that is true. When you give someone, for an example, an injection of fentanyl, it's rapidly cleared from the systemic circulation by redistribution. So, it hops into the brain very quickly and hops out of the brain equally as quickly, back into the systemic circulation, and then it's sequestered in the fat.

And then, making things even more confusing, and making you want to bang your head on the desk, is that fentanyl is highly bound to albumin, about 70 percent. And we will see in cancer patients, this extravascular leaking of albumin increase about 300 percent. So the albumin grabs the fentanyl and takes off for the hinterlands in the extravascular spaces. So, when we see this, this is why people aren't getting the effect that we might expect.

So, lots going on with fentanyl, particularly transdermal. Actually it's not a formulation that I'm quick to recommend, especially if somebody has pain that is changing very quickly, because it's sort of like spearing with the Titanic. It's

kinda hard to turn the boat with something that takes three to six days to truly get to steady-state.

Any tips from anybody else about fentanyl IV or transmucosal or transdermal?

Dr. Atayee: No, but it's really good to know about that albumin, because I have noticed that fentanyl isn't as effective at end-of-life care.

Dr. McPherson: Alright.

Dr. Herndon: Right-o.

Dr. McPherson: Alright my last ... I'm sorry, go ahead.

Dr. Uritsky: That's okay. I was gonna say, I work in an inpatient setting in a hospital, and there is a big difference in using fentanyl for sedation versus fentanyl for pain [inaudible 00:40:50] important to call out, because we see it used in the ICUs here very differently than we're using it for pain. And really because the dosing is quite different. So it's kind of challenging whenever we're making recommendations for pain, and you're only gonna give 25 or 50mcg/hr, that's like, yeah, we're not trying to sedate people.

So I think sometimes it's important to call that out. Because we had major discrepancies here in dosing for a little while, when they didn't realize pain dosing may be a little bit different.

Dr. McPherson: Great point Tanya. Thank you.

Alright, my last tip is one of my favorite things to talk about. They don't call me the Poop Queen for nothing. It's talking about constipation. Wow! What is constipation? Everybody's got a different definition. But certainly it has to do with frequency and straining. It's all about that, but patients with advanced illnesses very often do have constipation due to the drugs that we're using, most notably the opioids and their strong anticholinergics, their disease state, their diet, reduced physical activity. So a lot going on there.

So what is our normal treatment for constipation? Generally we use plain old Senna, which is a stimulant laxative, bisacodyl if we must, and I do like polyethylene glycol. The trouble with polyethylene glycol is the patient has to be able to swallow at least four, preferably eight ounces of a fluid to mix the polyethylene glycol in. Notably, Senna works better than Senna S, which combining with a docusate. That kind of just makes everything a red-hot mess. So don't even go there.

So, what if these don't work. What are we gonna do? So there are some newer agents introduced to the market, Lubiprostone, which is chloride channel activator, Linaclotide, a guanylate cyclase-C agonist, and now we've got this

whole crop of PAMORAs, peripherally acting mu-opioid receptor antagonists. So certainly everyone is familiar with methylnaltrexone, which we've had as a sub-Q injection for years and years, and now we have as oral. Movantik, which is naloxegol, and the new one is now naldemedine, which is also on the market. So these are medications that are opioid antagonists, but they're restricted to the periphery for a variety of reasons, either a [inaudible 00:42:51] or [inaudible 00:42:52] or it's got some long side chain that prevents it from crossing the blood-brain barrier.

So, of course we can give [inaudible 00:43:00] by mouth, we can use enemas or suppository per rectum. I do think it's important to keep an eye out for fecal impaction. I'm always concerned when I look at a medication history and I see Immodium followed by Senna, I have to question, "Are we coming or going here? So what's the deal?" So, often patients will get confused and say, "Oh, my gosh. Now I've got diarrhea. I better take Immodium." When in fact it's fecal content oozing around a fecal impaction. Isn't this lovely conversation here?

One home remedy that I always like to talk about is the frozen Vaseline ball. You take chilled Vaseline and roll it into a pea-sized ball, and then roll it in confectioner sugar. So it's just solid mineral oil. And for people who have kind of a high impaction and they're uncomfortable, have them swallow two or three several times a day. And a survey of almost 400 hospice professionals showed that two-thirds were very familiar with this, and 90 percent thought it was very effective in remedying this higher impaction. So, a little trick there for everyone.

Any other constipation tricks anybody has up their sleeve?

No, I think I covered the waterfront there.

So, Tanya, who's up next? Rabia?

Dr. Uritsky: Yep. It's Rabia's turn.

Dr. Atayee: Alright. Well, I have the difficult task of following the Poop Queen who just talked about Vaseline balls, but let's see if we can finish off these last two tips for the day.

Opioid selection, opioid monitoring, and opioid titration should be based on pharmacokinetics of each individual drug, with attention paid to onset of action, time to Cmax, half-life, and steady-state of those medications. Now if this PK language is making your head hurt a little bit, let's see if we can keep it simple.

So onset of action is kind of what is sounds like, is when you expect the drug to start working. Time to Cmax is when you would expect peak effect. These are both important concepts, especially when you're dealing with as needed or prn opioids. So, the approximate time to peak effect of an IV opioid is about 10 minutes. And the approximate time to peak effect of oral immediate-release

opioids is about 60 minutes. These are nice round numbers that make it easy to remember when you're at bedside. But obviously there's ranges.

Steady-state concentration is important for clinicians as it indicates a safe time to assess therapy and consider whether you wanna titrate the dose up if needed. And these are particularly important with long-acting opioid formulations. Five times a half-life is a pretty good accepted approximation of steady-state concentrations. And so, steady-state concentrations of the following long-acting opioids are as follows. Now again, keep in mind I've used nice round numbers to make sure that your head doesn't hurt, but also that it's easy to remember.

So, steady-state concentrations for oral immediate-release opioids and IV opioids is about a day. For controlled-release oxycodone is about one to two days. And for sustained-release morphine it's about two to three days. So if you started your patient on either long-acting oxycodone or long-acting morphine, hang tight for a couple of days before assessing whether it's at steady-state concentration and whether you need to make any adjustments.

Now, we're moving on to the long haul with the fentanyl patch and methadone. Fentanyl patch reaches 100 percent steady-state in about six days, or if you switch the patch every three days, it's two-patch changes. But the majority, about 80 percent of the patch, steady-state is reached in about three days, or one patch change. Methadone varies a lot, but on average, as a clinician, I wait until about seven days, and consider that steady-state before I assess whether I want to slowly go up on the methadone.

And keep in mind that beyond pharmacokinetics, when initiating methadone, and as you heard with Dr. McPherson, all the things with fentanyl, you do have to keep other things in mind. Key ones that I always tell people, but it's not limited to just these, is the presence of chronic pain when starting methadone or fentanyl patch, the conversion factor, which Dr. McPherson talked about with fentanyl patch, and drug-to-drug interactions.

How does that sound, group? So far?

Dr. McPherson: Awesome.

Dr. Atayee: Are you guys still with me? I didn't lose you on pharmacokinetics?

Dr. McPherson: I love it when you talk dirty Rabia.

Dr. Atayee: Alright. Now moving on to our final tip of the day, which is secret side effects. We like to call them secret ... Some of them are common ... But they're just not commonly known or thought about adverse effects. And we think it's important, especially as we're using certain types of medications in palliative care.

So, as we all know, rarely do medications exist without any side effects. And the goal is always, "Let's use a medication where the efficacy is a lot more than the adverse effects." An additional factor we have to keep in mind, that others have alluded to earlier, is that in the palliative care setting, we're using medications off label. And at different doses and commonly at lower doses than the FDA approved doses. And you have to keep in mind that the side effects may also be different because some side effects are dose dependent.

So, let's talk about being mindful of these secret side effects at palliative care doses. Ondansetron. We kinda talked about ondansetron, and even though I share Dr. McPherson's sentiments, that it's not good for a whole lot, ondansetron still gets used a lot, especially for nausea and vomiting. And it's not commonly known that ondansetron causes headaches and constipation. So for your patient who's on an opioid therapy and complains of headaches, less ondansetron, not more opioids may alleviate their headache.

And in the setting of opioid-induced nausea, vomiting, and constipation, metoclopramide, or as Dr. Uritsky would say, olanzapine, would be a better antiemetic than ondansetron. And although I love metoclopramide, and before we all consider putting it in the water, let's keep in mind that metoclopramide also has its own secret side effects. If you'd start your patient on metoclopramide and you notice restlessness in your patient, you may be witnessing dopamine-induced akathisia. You know how you'll know for sure? Is if you stop or hold the metoclopramide and the restlessness improves.

We've had a few cases where the patient had restlessness for a couple of days, and we really thought it was anxiety or other things going on, but then when we held a few doses of the metoclopramide, that restlessness went away. So, although I love metoclopramide, I am aware of the secret side effect now.

In the palliative care setting, scopolamine and promethazine offer alternative to the oral route for treatment of nausea and vomiting. Scopolamine comes in a patch that you can swap behind the ear, and promethazine is available in oral but also suppository and IV. But the next time you want to slap on a Scop® patch or recommend Phenergan suppository in your 70 year-old patient, consider that both these medications have anticholinergic side effects, notably, sedation, dizziness, delirium, and constipation. So, all of that would not be good in your palliative care or hospice patients, especially in the elderly population.

We've talked a lot about constipation today, and one of the things I find, that seems very tempting for our medical residents, is to use Fleet® Enema for constipation. But keep in mind that there's a 96 percent, that's almost guaranteed, that it will cause hyperphosphatemia, even at normal renal functions. But then it becomes even more problematic at renal dysfunction.

So, all the things that Dr. McPherson talked about, the non-traditional options, those Vaseline balls, or just simply tap water enema is just as effective. So, let's

put away the Fleet® Enema aside. Alright, continuing the poop talk because we can't get enough, in the setting of constipation, when you have a choice between lactulose and MiraLAX®, and as Dr. McPherson said, you got to be able to have oral intake. So if you have oral intake and you're deciding should I lactulose or MiraLAX®, which one's my osmotic agent of choice, I would advocate you start with MiraLAX®, because lactulose has a lot of flatulence, and in fact, greater than 20 percent of patients experience it.

And if your patient's on long-term opioids ... Now we're talking about months to years ... Be sure to monitor for long-term side effects of these medications, such as immunosuppression, hormonal or endocrine dysfunction.

Alright. Rounding off the last couple of secret side effects, and then you'll be in on all the secrets. Tramadol. I'm in the camp of tramadon't, but if you like tramadol and you really, really want to use it, besides serotonin syndrome, which is known but doesn't commonly happen, we have to worry about hypoglycemia, which is emerging. And hypoglycemia to the point where it's causing hospitalization.

Gabapentin. We all like our gabapentin as our first line neuropathic pain agent, but it has up to 10 percent risk of causing peripheral edema. In fact, today I had to stop gabapentin on someone who after a dose titration from 100 q8 to 200 q8, so not really dose-dependent, she developed edema in her periphery. And so we had to stop the gabapentin.

TCAs. Tertiary TCAs, the one that everybody knows a lot about, amitriptyline, or Elavil, can cause a lot of anticholinergic side effects. And we all know that that isn't good in our palliative care patients. If you're gonna need to use a TCA, use the secondary means of TCA including nortriptyline or desipramine. And keep in mind that those still have some anticholinergic effects, just less.

And Dr. Uritsky, I know you love olanzapine, and you wanted it in the water too, but we do have to worry about greater than 20 percent orthostatic hypotension in these patients.

I think that's all the secrets I have for today. Anybody else want to add to that?

Dr. McPherson: Well, you sure spilled the beans there, girl.

Dr. Atayee: And these are secrets that we'd like you to thread, not keep them a secret, because they are good tips to remember.

Dr. McPherson: That's right. Any comments from anybody else as we wrap up?

Alrighty. Well, I'd like to thank Dr. Uritsky for heading up this motley crew here. She's the lead author on this paper, "Ten Tips Palliative Care Pharmacists Want the Palliative Care Team to Know When Caring for Patients." Other authors are

Rabia Atayee, Christopher Herndon, Kashelle Lockman, myself, and Christopher A. Jones. So I would like to thank our guests, and thank you for listening to Palliative Care Chat, our podcast. Again this is Dr. Lynn McPherson. And this presentation is copyright 2018 University of Maryland. For more information on our completely online Master of Science and Graduate Certificate Program in Palliative Care, or for permission requests regarding this podcast, please visit graduate.umaryland.edu/palliative. Thank you.