Public Comment to the Committee to Assess the Available Scientific Data Regarding the Safety and Effectiveness of Ingredients Used in Compounded Topical Pain Creams Meeting 2. May 20, 2019.

Jennifer: Okay. Thank you so much. I'm Jennifer Winegarden. I'm a hospice physician, and I've practiced hospice full time for 11 years. I wanted to address six questions that came up through the day through my perspective dealing with patients who are dying, who are not going to have a lot of aggressive care. They're not going to have a lot of work-ups, and they have very few options.

One of the questions was, "How do physicians get trained in use of topical adjuvants? How do we know which of these adjuvants work? How do we know which ones are safe? How do we care for patients with diminished options or those that can't move in contrary to what the last three physicians said about movement, exercise, things like that?"

My findings, oh yes, about pain associated with lesions and patients with higher levels of pain. In my experience in my patient population, if I can't control their pain, then what happens is that they get sent to the hospital as a general in-patient in another level of hospice care. What has happened when I've done that is they get put on IV opioids, and they stay on higher and higher doses until they die, most often from the opioids, not really the cause of their decline.

How I got trained is that palliative physicians talk to one another. 10 years ago I said, "I have a case. I can't, no matter what I've tried to use, opioid and adjuvant, nothing is working." A head of a residency program said, "I want you try Ketamine, Clonidine and Gabapentin together in a cream. Here is a PhD in compounding pharmacy medicine that you can collaborate with in Michigan."

I started doing that over 10 years ago. In the time since then, my N population is well over 200 patients, maybe over 300 patients using things like primarily Ketamine. How do we get trained? Those of us who are in palliative medicine often just talk to each other and these wise compounding pharmacists.

How do we know what works? Simply, as a patient's pain is going to increase the closer they get to death and we start these medications and we can achieve comfort like in the case Dan Carr shared this morning, which was my case, that's how we know that they work.

How do we know it is safe? Again, my N is well over hundreds of patients. I've had one reaction where a patient said their pain actually increased with the cream, and I've had maybe two patients out of 300 that had some erythema.

We know from our experience at the end of life that pain, when it's high, I'm talking well above four, I'm talking eight, nine, even 10 out of 10, that that cream is going to work better than the cases that you're talking about at a pain level of three and four. I also know that when that pain is

associated with a lesion, cancer growing through the surface of the skin, areas that have been really compromised through your decades of health problems, that that compounded cream is going to work best.

I also know from my own personal research that there is a lot of preclinical data that nobody talked about today. That preclinical data is pretty powerful when you look at the medications that are used the most. Ketamine, Clonidine and Gabapentin all have been shown to reverse tolerance. They've been shown to reverse opioid-induced hyperalgesia.

I've had cases where I've used IV Ketamine and reversed opioid-induced neurotoxicity, bringing about not just pain relief but a safe and peaceful death. Anyway, I wanted to make these comments. None of these things were said during the day, and they relate to end-of-life care. Thank you.

Man 1: Can you tell whether there's a systemic blood level of those three or whether it's non-systemic? Is that possible to know the answer?

Jennifer: That's been a question that I've looked into a lot, especially I've had two publications. I have a third one that's hopefully going to be very soon on this. I've dug into a lot of the preclinical data. That's where I thought the question that we tried to get the answer for about five minutes today about that really has its answer.

Even when they're doing it in the laboratory, they're doing it in the hospital, and they're checking those blood levels, they're nearly nothing. A lot of the published studies show that if you use topicals you have the highest concentration in the tissue. It's right there where you want it in the tissue you want it, and you don't have to worry about the high blood levels because really, they're not there. There have been a lot of people who've looked at that, and the blood levels are miniscule.

Man 1: You're primarily treating lesions?

Jennifer: Yes. My best response is with lesions. I even have an anecdote that I would never share, except I think it's important. I have a lesion here on my elbow that caused a neuropathy, and I was losing the use of my left hand. I did an N-of-one experiment on myself.

My orthopedic surgeon who was waiting to do surgery gave me Voltaren Gel. If you haven't used it, it's kind of nasty. It's greasy. It has a bad smell, and it did zero. It did absolutely nothing. Again, I had a distinct lesion. It was very painful. It would wake me up probably 10 times a night. If I just moved my arm during the day, I'd get it as just zinging pain, I mean nine, 10 out of 10.

Then I ordered my own, what I would use as a palliative care doctor. I ordered the Ketamine 10 percent, Clonidine 0.02 milligrams and the Gabapentin six milligrams all per one ml. I really was skeptical because I knew it was large, and I knew it needed to have surgery. I couldn't move the distal part of my hand.

Within 30 minutes, as my patients have told me by the hundreds, within

30 minutes my pain was down and I could sleep through the night, but I made myself do the trial. I would go back to my gel, to the gel from the orthopedic surgeon, the N-set and then go back to my adjuvant gel and/or cream. It was no different. I would have either seven, eight, nine out of 10 pain or I would have the complete pain relief until it wore off at about eight hours.

Woman 1: If that were available as a cream that wasn't compounded but was just over the shelf or by prescription, would it be different or would the concentrations have to change so much that it can only be done through compounding? I'm just curious.

Jennifer: My belief is that this is something that I would like towards seeing as manufactured because I've done it in patients again with very significant pain related to very significant disease process. In my N of, let's call it 300, I'm getting well over a reduction of four to five out of 10 in pain.

John: [indistinguishable]

Woman 1: Having said that, we have made no conclusions to date. Just want to make that clear.

Jennifer: John, I did write up an RCT myself. I was going to do it, and it was very similar to that. I failed to do it at the end because I thought I had too many confounders with my patients having different kinds of cancers or different kinds of lesions and what not. Then I thought of it carrying over past eight hours, but I do think it's a veiled study. I think it would be positive.

John: The trick is N-of-one because then patients are their own controls and all the confounders go away, except for the progression of time.

Woman 1: Okay. Steven, you can finish up and then Joyce had a bit.

Steven: Okay. I'll mix a product GMP for you because you have to have a GMP product to do this trial.

Woman 1: Alright. Joyce?

Joyce: Why those three drugs together?

Jennifer: Yes. That's a great question. At first, the reason I started that way, Joyce, was because I was simply advised that way. Then when I talked to my pharm D about it, he said, "I think that is a good choice of those three drugs." When I did my own research, and that is going through all of this data, I found that it's just a beautiful combination if you hyper-polarize the afferent, the key is the primary afferent neuron.

If we can shut it down, if we can reduce the neurotransmitters, if we can reduce the synapse at the posterior dorsal horn and we can reduce central sensitization and spinal wind-up, then we've got something very powerful. That is what I'm seeing it clinically, and I'm reading about it preclinically,

but nobody has proven it. My patients prove it every day.

Joyce: You need all three?

Jennifer: I am afraid to pull out one, and since my hospice is willing to absorb all these costs for me, I can, but my money is all on the Ketamine. You've got an anti-inflammatory. You've got reduction of inflammatory markers, neurotransmitters and serotonin and norepinephrine, and that doesn't hurt. Then you've got the full NMDA antagonism. It's a win.

[END OF TRANSCRIPTION]