Cyberseminar Transcript

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Session: Effectiveness of Opioids for Chronic Pain—the SPACE Trial in Context

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Molly: We are at the top of the hour. So at this time, I’m happy to introduce Dr. Cathie Plouzek joining us from Central Office. She is the Scientific Program Manager for Care of Complex Chronic Conditions and she is going to introduce our award-winning speaker. So Cathie, I will turn it over to you now. I’m so sorry, give me one second here. I, okay Cathie now you’ve got audio.

Dr. Cathie Plouzek: Okay, thank you. It’s with great pleasure to have this opportunity to introduce Dr. Erin Krebs, who will speak with us today on her Chronic Pain and Opioid Prescribing research. Dr. Krebs is part of Health Services Research and Development Center for Chronic Disease Outcomes Research. Her professional goal, as a General Internist and Health Services Researcher, is to improve the management of chronic pain in primary care. She currently leads a Health Services Research and Development nationwide study of VA patients on long-term opioid therapy, and a Patient-Centered Outcomes Research Institute, PCORI, funded VA multisite trial testing approaches to improve pain and reduce opioid use among Veterans in high dose long-term opioid therapy. Among her achievements is the 2018 Health Services Research and Development Best Research Paper of the Year Award. The award honors a single article or collection of articles resulting from Health Services Research and Development or QUERI funded investigations that involve Veterans and yield results that are important to Veterans’ healthcare and to the VA healthcare system. Dr. Krebs’ article, Effect of Opioid versus Nonopioid Medications on Pain-Related Function in Patients with Chronic Back Pain or Hip or Knee Osteoarthritis Pain the SPACE Randomized Clinical Trial, was published in JAMA in March 2018. Funded by Health Services Research and Development this landmark study was the first randomized trial to report long-term pain function and quality of life outcomes of opioid therapy for chronic pain. I’m pleased to welcome Dr. Erin Krebs to present the effectiveness of opioids for chronic pain, the Strategies for Prescribing Analgesics Comparative Effectiveness, SPACE trial in context. Over to you, Erin.

Dr. Erin Krebs: Thank you so much. I believe you all can see my slides at this point.

Molly: Yes, we can.

Dr. Erin Krebs: And it looks like I can advance them as well. So that’s a great start here today. To start with disclosures mostly, just to let you know my funding is from VA, NIH, and PCORI. I do not have commercial financial relationships. And because these Cyberseminars tend to have a really diverse audience, I wanted to just start my talk today with a poll question. And I will actually turn this right back over to Molly to bring the poll question up.

Molly: Thank you. So for our attendees, as you can see on your screen, you do have the poll question up. So we’d like to just take a mon, a moment, pardon me, and find out what is your primary role related to opioid prescribing for chronic pain. And your answer options are prescribing clinician, non-prescribing clinician, researcher, student or other. And you can just go ahead and click right there on your screen next to your corresponding response. It looks like we’ve already had three-fourths of our audience reply, that’s great. So I’m going to give people just a few more seconds to get their responses in. Okay, we’ve got about an 80% response rate, I’m going to go ahead and close this out and share those results.

Nine percent of our respondents selected prescribing clinician, 28% non-prescribing clinician, 44% researcher, 1% student and 18% other. So thank you to those respondents, and Dr. Krebs, I will turn it over to you one last time.

Dr. Erin Krebs: Okay, fantastic. So seeing just who’s on the call that actually really helps, and I am happy that I did. When I put this together, I did try to make it broadly applicable to people regardless of their focused expertise on this topic or whether they’re a clinician or not. So I hope this will be relevant to many of you on the call. So I’m starting with two basic slides, and the first one is just briefly defining chronic pain. So this study is about chronic pain, and a common definition of that is persistent or recurrent pain for at least three to six months. Now, studies use variations on this definition, and that’s why you see so much variation in the number of people thought to have chronic pain. In general, using just this duration-based definition, perhaps 20 to 30% of U.S. adults or 40 to a hundred million people experience chronic pain. Importantly, though, chronic pain is not necessarily life-limiting or severe, so most of the people who have chronic pain are actually not limited by it. A more relevant definition for this particular study is high impact chronic pain, and that has been defined as pain that is chronic, meaning persistent or recurrent for at least three to six months, and causing activity limitations or participation restrictions. So really disabling chronic pain. This is a smaller proportion of U.S. adults, perhaps about 5%, closer to 10 or 11 million adults, and those are the people who really are the ones who would be candidates for opioid therapy.

A brief word on treatments in general for chronic pain; chronic pain is not one thing. I provided a broad definition but within that definition, there are many different chronic pain conditions and those may have different treatments. I like to think of treatments as falling into two main categories when we’re talking about chronic pain. The first category is treatments that target disease-specific factors. So here the specific pain-related diagnosis matters very much, and an example of this would be joint replacement in someone with severe knee osteoarthritis and chronic pain related to that. You know, joint replacement is a specific treatment for this specific degenerative joint condition. However, that’s actually not the way most pain treatments work. Most treatments for chronic pain actually target common pathways that are involved in a variety of different chronic pain conditions; pain sensation, pain maintenance, pain amplification, or disability, development of disability related to pain. So, examples of these kinds of more general treatments include exercise therapy, for example, that might be targeting body mechanics, strength, activity tolerance or fear of movement, pathways that could be involved in a number of different types of pain conditions. Opioid therapy likewise is one of these common treatments that targets a common pain pathway, specifically, for example, opioids target mu receptors that modulate transmission of pain signals.

Those are my two background slides. So now I’m going to move to the meat. This is the paper that won the award that we’re here to talk about today. And I will just give you the bottom-line up front, because there’s no reason to hold it back as a surprise. We found that opioid therapy was not superior to nonopioid medication therapy for chronic back pain or hip or knee osteoarthritis pain over 12 months. There is the bottom-line, and now I will go into much more detail.

First, I just want to provide one background slide that is most relevant to this study. This is a, just a screenshot here from part of the VA DoD opioid prescribing clinical practice guideline from 2010. And this is the guideline that was in effect when we were developing the SPACE study plan. The recommendation, the first recommendation actually in that guideline is that opioid therapy was indicated for moderate to severe pain that has failed other indicated therapeutic interventions. And that was the recommendation that was based on mostly expert opinion at the time. We designed the SPACE trial really to test that recommendation, and to look at patients who would be candidates for opioid therapy according to the guidelines of the time. I imagined our two treatment groups as representing two very distinct philosophies of pain medication prescribing for patients who did not initially respond to nonopioid medications. You know, some clinicians at that point would initiate strong opioid medications, and others would prescribe everything except for opioids and really tried to avoid strong opioid medications. So we tried to kind of replicate that, those two different philosophies in our treatment groups.

The overall objective of the SPACE trial was to compare benefits and harms of opioid therapy versus nonopioid medication therapy over 12 months. Among patients with chronic moderate to severe back or osteoarthritis pain despite analgesic use. The italicized words here are just reflecting that guideline recommendation that we wanted to test, and we focused specifically on chronic back pain and chronic hip or knee osteoarthritis pain because those are the two most common pain diagnoses in people treated with long-term opioid therapies, both in VA and in general. The design for this study was a pragmatic randomized trial with blinded outcome assessment. Pragmatic here means that this was a trial designed to as much as possible be applicable and relevant to real-world practice. So, when we could we tried to make elements of this study consistent with what would be done in the real world. Of course, not the randomization part, that’s what most clearly distinguishes, you know, a trial from real-world practice, and that’s inherently artificial, but other decisions like who we enrolled and how we ran the interventions were designed to be pragmatic in nature. This study, because of its pragmatic nature, could not be fully blinded, I’ll talk about that more later, but the patients knew what group they were in and so did their clinicians. Both study clinicians and, you know, anyone could look in CPRS and see what treatment group these patients were assigned to and what medicines they were receiving in the study. The outcome assessors who did the actual interviews to determine how patients were doing during the trial, those folks were blinded.

This figure shows the basic structure of the study. We enrolled 240 VA patients. We randomized them in equal numbers to receive either opioid medications or nonopioid medications for 12 months. And during that 12 months, we treated them actively and we followed them assessing their outcomes. The primary outcome was pain-related function. The second main outcome was pain intensity, and the main adverse outcome was bothersome patient-reported side effects.

For eligibility criteria, we tried to include patients who would potentially receive opioids in practice. So if they had a doctor who was, you know, following that VA guideline and inclined to start opioids, they would be candidates. For this reason, we really tried to keep exclusion criteria to the minimum necessary, primarily for safety. So we were not trying to find ideal opioid candidates, we were trying to find typical opioid candidates. I mentioned why we chose chronic back pain and hip or knee osteoarthritis pain as our main conditions, because they’re the most common ones for which people take long-term opioids. We required patients to have moderate to severe pain severity and functional interference despite using medication. So they had potentially failed nonopioid medications, so this was the idea here. We did not assess whether, you know, how much they’d had in terms of prior non-medication treatments. For our major exclusion criteria, the big one, we excluded people who were already on long-term opioid therapy, which we defined as around the clock opioids. So patients in the study weren’t necessarily opioid naïve, some of them had had some opioids, you know, definitely in the past and sometimes recently, but at least we did not think they were physically dependent on opioids at the time of entering the study. And we excluded everyone we thought had an absolute contraindication to opioid therapy. So, you know, if they had, you know, an active alcohol use disorder, for example, they would be excluded. However, we did not exclude people with severe mental health conditions, severe medical conditions or past substance use disorder. So if someone had been treated for alcohol use disorder and currently did not have active alcohol use disorder, we would bring them into the study.

So our interventions were opioid therapy and nonopioid therapy. All patients in both groups received individualized medication management within their assigned group. And this is a big part of what made this study pragmatic. You know, many classical clinical trials would assign to one drug versus placebo or a second drug and they’d be trying to target a fixed dose of each drug. That’s not how the real world works though, in reality, we work with patients to find medication treatments that work for them, we adjust medications according to response and that’s what was done in this study. So patients in both arms did have a clinical pharmacist care manager they worked with. I’ll talk about that more later. And that clinical pharmacist worked with the patient to target improvement in their functional goals and in their PEG score, or a pain measure. They were treated with a prescribing strategy that had three different medication steps, and I’ll show that on the next slide.

This table shows the prescribing strategies for each group in three steps. Opioid group on the left, nonopioid group on the right. And as you can see, each group had a menu of medication options. In general, we tried each step before moving to the next, but where patients started depended on what they had previously tried. So if a patient had previously had a good try of acetaminophen, or they were already on it and it wasn’t working, we wouldn’t redo that medicine we would move on to a next option. As you can see, those are all VA formulary options, we didn’t have anything experimental or unusual in this study. And the asterisks just indicate the preferred initial medication, so unless there was a reason not to, we started with morphine IR in the opioid group and acetaminophen in the nonopioid group.

This figure shows our study flow. It’s a little abbreviated. We enrolled 265 patients from 2013 through 2015. We randomized 240. We did lose a few before randomization. Of the patients who were randomized, they were assigned in equal arms, or in equal numbers to the opioid arm and the nonopioid arm. All but one received the intervention to which they were assigned. And then we followed them over time. We did outcome assessments every three months. This figure just for simplicity only shows the final follow-up time point. We were able to assess all but three patients in each group at 12 months, which is really impressive, I’m super proud of my team did a fantastic job of following up with everyone, and our patients were just committed to this project. We were able to include an analysis all but two patients. So all but two patients had at least one post-randomization outcome assessment.

Briefly, our participant characteristics are similar to a lot of VA studies. Patients were on average in their late 50’s, 13% were women, which is about twice the representation of women in the general VA patient population. About two-thirds of the patients in the study had back pain as their primary pain problem, and about a third had hip or knee osteoarthritis pain as their primary pain problem. And primary is emphasized here because many of these folks had multiple pain conditions. Some had both back pain and osteoarthritis pain, but we asked people to name their primary pain condition, and that was what we used for the inclusion criteria and for this stratification variable.

Since the study was not blinded, we were really interested in knowing what patients preferred prior to starting this study and what their perceptions were of our treatment groups. So we asked patients, this is after enrollment before randomization. So they don’t know what treatment group they’re going to be in yet, but they have had all the information that they need about the two different treatment groups and the study overall. We asked them which treatment group they would prefer, understanding that they weren’t going to get a choice. And about half of them said there’s no, they had no preference. You know, I don’t know if this is surprising or not. I think a lot of patients maybe aren’t sure what they want, so maybe it’s not surprising. Of course, these are people who were willing to enroll in a randomized trial, so maybe they’re a little bit more likely than your average person to agree to the coin flip method of determining what group they get into. Of those who did have a preference, a few more preferred opioids than nonopioids. If you looked at perception of the treatments, overall patients regardless of what group they preferred or what group they ended up in, patients thought opioids were more effective than nonopioids. We asked them to rate from zero to 10, not at all effective to most effective possible, the two treatment groups. And on average opioids were thought to be close to an eight, nonopioids thought to be close to a six. So in general, people enrolling in this study did think opioids worked better than nonopioids.

We did have a qualitative component to this study, and there’s a companion paper that Marianne Matthias authored, published in the Journal of Pain that goes into our qualitative assessments in more depth. But this is just a quote from that qualitative paper, and it illustrates one of our participants who wanted to be assigned to the opioid group, why he said that he wanted the opioid group. He said, “There’s a reason it’s a controlled substance. Usually because it’s better. So in my mind, when you’re in serious pain you need serious medication.” On some level, I think this is a fairly representative quote.

So without further ado, here’s our primary result. Our primary outcome, pain interference with function, assessed with the Brief Pain Inventory interference scale. This slide shows on the horizontal axis, months in the study, and we did assess this every three months, and then on the vertical axis, the mean BPI score. And what you can see here is the opioid group in orange and the nonopioid group in blue track along together over the course of the 12 months. There’s no numerical or statistical difference between the groups in terms of pain interference with function.

This is our second main outcome, pain intensity, measured with the mean Brief Pain Interference severity score. And here you can see that over time opioid group in orange is a little higher than the nonopioid group in blue. That was a small and statistically significant difference favoring the nonopioid group, because here lower scores are better, higher scores mean worse pain.

And this is our main patient-reported adverse outcome, medication, the number of bothersome medication side effects. Pretty clear throughout this entire study that patients in the opioid arm had more bothersome medication side effects.

We were not thinking we would be powered to assess for adverse events differences, and indeed we did not see them. There was no difference between the groups in the rates of emergency department visits or hospitalizations. Each group had one event, one ED visit or hospitalization that was thought to be related to analgesics, and we did not have any death, addiction, or diversion events. We did look for those carefully and did not identify any in either group.

This quote is again from the qualitative evaluation study. I think it illustrates how sometimes the story is much more complex than what the numbers can tell us. This was a patient who was in the opioid treatment group and who did respond. So according to the quantitative measure she had a clinically relevant improvement in her pain-related function on opioids, but she said in retrospect, “I’m glad I’m not on opiates anymore. They were effective, but it felt like I was living my life in a sleepy stupor. I did not like being tired and, you know, I could lay on the floor and just fall asleep. My quality of life, I thought, diminished because of the opiates.”

So in summary, SPACE results found that opioid therapy was not superior to nonopioid medication therapy over 12 months. We found no difference in pain-related function between the groups. Nonopioids had slightly better pain intensity and nonopioids led to fewer bothersome side effects.

So the primary implication, of course, the one that got all the press is that our results do not support initiation of long-term opioid therapy in patients who have moderate to severe chronic pain despite analgesic use. So this really refutes that prior opioid guideline recommendation.

The second implication, though, is that results do support active nonopioid medication management in patients with moderate to severe pain despite analgesic use. And here I’ll just highlight the rates of improvement that we saw, specifically in the nonopioid group. So remember, we recruited people who could be considered to have failed the nonopioid medication therapy, and indeed many of the people in the study thought that they had tried everything and nothing was working. Nonetheless, that nonopioid group, more than half of them had a clinically significant improvement in their pain-related function and in their pain intensity. So how did we get that?

Well part of the story, I think, is that both groups in this study received treatment using a telecare collaborative management approach, that pharmacist care manager that I briefly mentioned before. This is an approach that was previously studied in a VA randomized trial led by Dr. Kurt Kroenke at the Indianapolis VA. That trial was published in JAMA in 2014 and it compared telecare collaborative management, much like what was used in the SPACE study, versus usual primary care for chronic pain. And about twice as many patients improved with the telecare collaborative management, for a number needed to treat a four. There were three key features of this TCM model, and I’m just going to walk through each of them quickly; a care manager with expert back-up, structured reassessment, and a stepped approach to analgesic management.

So the first feature, this was again the model tested in that trial by Kurt Kroenke, and then we used this model in SPACE, but again, we kind of controlled for this model because we did this in both arms. So the first feature is the pharmacist care manager. The figure here shows in white circles the preexisting relationships, the patient with the primary care team. Of course, there were probably a lot of other people involved in their care but trying to keep it simple here. The pharmacist care manager is directly interacting with the patient, and also as needed with the primary care team to coordinate care. There’s a consulting expert physician who’s working with the pharmacist care manager having regular meetings to talk through the case and any challenges that are coming up and the treatment approach. According to the SPACE protocol, visits between the patient and the pharmacist care manager were monthly at first and then every one to three months after that. In SPACE the mean number of visits over 12 months was nine in both of the treatment groups, and on average patients had three in clinic visits and six telephone visits.

A lot of what was done during those visits was a structured reassessment of how patients were doing with treatment changes. And then addressing any additional changes in their treatment. So the first aspect of the structured reassessment is progress toward individual functional goals. At the first visit with the patient the pharmacist care manager worked with the patient to identify what their priorities were in terms of how they wanted their life to improve with improved pain management. And then at each follow-up visit, the pharmacist returned to that goal to see how the patient was doing in relation to the goal. We also used three structured measures; the PEG for pain, which is three items, a past week rating of pain on average, pain interference with enjoyment of life, and pain interference with general activity, and then the PHQ-2 for depression, questions about two major depression symptoms in the past two weeks, and the GAD-2 for anxiety, questions about anxiety symptoms in the past two weeks. And these were assessed at each follow-up visit and used, you know, reflecting back on the answers to determine how people had responded in terms of their prior treatments and think about how any future treatments should be made. Treatment changes excuse me.

The third feature of this model is a stepped analgesic management. And I previously showed you in SPACE what the stepped approach looked like for each of the two groups. The opioid group and the nonopioid medication group, both of them used VA formulary medications in three steps. And the medications were individually actively trialed. So, there was, you know, when a medication was started it was titrated up to what we thought would be an appropriate effective full dose. And if it did not work, if it was not well tolerated, if there was not improvement, it was tapered or discontinued. So it was really an active medication management strategy. This incorporated kind of an informal shared decision-making approach that was based on the patient preferences, priorities and just going back to those measures that I mentioned on the prior slide. In the nonopioid group in SPACE, patients tried a median of four drugs over the 12 months. So I think this approach really, it really addresses the clinical inertia that can happen. I think in practice too often we start medicines and we never really reevaluate the response to them. We often just kind of continue things and pile new medicines on to old without reevaluating effectively and stopping those things that aren’t really making a difference.

Just to give you a sense in the nonopioid arm what patients actually got. The most common drugs that were tried during the study were topical lidocaine, acetaminophen, naproxen, nortriptyline, and meloxicam. It shouldn’t be surprising that those were all in the first two steps of the prescribing strategy. And what the figure shows is actually dispensing of study medicines over the course of the study, from month one on the left to the end of the 12 months on the right. It’s just a count of prescriptions on the vertical axis. And so, you know, at the beginning the most common prescriptions were NSAIDs, Nonsteroidal Anti-Inflammatories, including naproxen and meloxicam. And then I think ibuprofen was probably the third most common. For both the NSAIDs and for acetaminophen what you can see is that the high point is the beginning. You know, these were step one, and a lot of the patients who initially started those medicines didn’t continue them. And so there’s a decrease and then a flattening of their use over time. In contrast, topical medications start lower in month one. These were step two medicines, so often we didn’t end up trying them until month two, three or four. And then there is a leveling off of those medicines.

So now that I’ve given you some of the SPACE details, I’m going to just talk a little bit about context. How do the SPACE results fit into what else we know about opioids for chronic pain?

So this is what we knew before SPACE. It’s not like SPACE was the first trial of opioids, there had been quite a few trials of opioid therapy. Almost all of them were classical clinical trials comparing a single opioid, mostly to placebo, over a short period of time. So generally speaking the majority of the trials of opioids versus placebos have been very short-term, you know, eight to twelve weeks in duration. And from these studies, it’s clear that opioids do decrease pain more than placebo, but the difference between opioids and placebo is actually quite small. So from meta-analysis of opioids for chronic back pain, the difference between opioids and placebo is about 10 points on a zero to 100 scale. For hip or knee arthritis about seven points on a zero to 100 scale. This is a small difference, and much less than what most patients would expect, or what most clinicians would expect from opioid therapy. In terms of the gaps before SPACE, really very little known about opioids compared to active treatment because there’s been far fewer studies of opioids versus any active comparator, and really very little data on opioid effectiveness for more than three months. And so that’s, those were the main gaps that we were focused on with the SPACE trial. A 12-month study comparing opioids to what we thought was the most reasonable, most direct comparator nonopioid medications.

Since SPACE, there have been a number of updates, meta-analyses, and systematic reviews. This is one that came out at the end of 2018, published in JAMA. A comprehensive systematic review and meta-analysis of trials that compared opioids to a nonopioid control for chronic pain. This review excluded studies that had follow-up for less than four weeks. So at least the very short term, very, very short-term studies were not included. They found 96 trials of one to six months duration that were included.

And this is just a summary of their main findings, consistent with prior meta-analyses. They found that opioids were slightly better than placebo, in terms of pain it was about 0.8 points on a zero to 10 scale, so eight points on a zero to 100 scale would be analogous. For physical function an even smaller difference, hard to imagine how this would be clinically relevant, about two points on a zero to 100 scale, the difference between opioids and placebo in this meta-analysis. Interestingly they did some sub-analyses, and the effects of opioids were smaller in studies that had longer follow-up. I think not surprising for those of us who work clinically with opioids, we know about tolerance and how that probably affects outcomes. And they also looked at the relationship between opioid dose and strength and outcomes of pain and function, and there was no relationship, so evidence of a dose-response in terms of opioids. There were nine trials, they identified, that compared an opioid to an NSAID, and they did not differ in terms of outcomes.

So another question I think that comes up almost always, when people, when I’m talking about the SPACE trial, is what about patients who are already on long-term opioids? You know, these patients were excluded from the SPACE trial and therefore the SPACE results do not apply to these patients. So we don’t, SPACE really focused on initiation of opioid therapy so an implication is don’t initiate opioids, but you know, if opioids are already initiated what do we know there?

For this, to just talk about this question I’ll present results here briefly from a systematic review of patient outcomes and dose reduction or discontinuation of long-term opioid therapy. This was a systematic review led by Joe Frank, a VA investigator at the Denver VA, and you see a lot of other VA names on the author list there. This meta-analysis, or I should say this systematic review was really designed to be very liberal in terms of inclusion criteria because there are so few studies that have looked at dose reduction or discontinuation of opioids. So studies were included if they reported outcomes of dose reduction or discontinuation and a broad range of designs were included. So not just randomized trials as in the prior systematic review but also observational studies. Eleven randomized trials were included, 56 observational studies were included and most of those observational studies were uncontrolled observational studies. A wide variety of interventions were evaluated in these studies. The largest number were interdisciplinary pain programs, about 10 studies looked at buprenorphine, about six studies looked at behavioral interventions, and then smaller numbers looked at a lot of other various interventions.

This is the bottom-line findings from this systematic review. The good news here it looked like interdisciplinary pain programs and behavioral interventions may be effective in reducing opioid doses, and it looked like pain function and quality of life may improve during and after opioid dose reduction. So all of the studies that looked at those outcomes had positive findings of improvements. However, the downside is that the overall quality of evidence was very low. And this is, again, going back to the study design. Most of these studies were uncontrolled observational studies, and the few trials that were found were quite small.

Considerations in interpreting the findings from this review are that findings really do only apply to patients who agreed to participate. All of the programs evaluated here whether they were a trial, or you know, an intervention, a clinical intervention, patients were voluntarily involved in those studies, in those interventions. And really none of these studies reported much about any adverse effects or risks of tapering, so just inadequate evidence to evaluate that. And then a third important consideration is that the promising interventions in this review were mostly quite intensive involving close follow up and often interdisciplinary support for patients.

So coming to an end here in terms of conclusions. SPACE found no advantage of opioids over nonopioid therapy among patients who previously failed nonopioid therapy for chronic pain. In context, I would say these results are consistent with evidence from other studies. I think the body of evidence suggests that opioids have small benefits compared with placebo that diminish over time and are not related to dose or strength. And further, it seems that opioids are not superior to other analgesic medications.

Also in context, the SPACE results are supportive of current opioid guidelines. I mentioned how they really refuted the old VA guideline, but the current VA guideline recommends against initiating long-term opioids for chronic pain and SPACE’s results really support that recommendation. Likewise, the CDC opioid prescribing guideline states that nondrug therapies and nonopioid medications are preferred over opioids. That’s also supported by the SPACE results. Importantly, as I mentioned, SPACE results do not apply to patients already on long-term opioids. I would say that if anyone says we have an evidence opioid reduction or opioid tapering strategy you should question that because we have so little evidence about opioid reduction or tapering. Really, what we know is limited and so, you know, we are engaging of tapering, it’s important, but we need to be humble about that, and I think tapering approaches should be cautious, individualized, and collaborative given really what we know or don’t know there. That’s the biggest gap at this point and time.

I do have one bonus slide. I always feel like if I spend 45 minutes or an hour talking about medications for pain that I have to say that medications are not the first line treatment or the best treatments for chronic pain. We know a lot about how to treat chronic pain, and really if you look at chronic pain management guidelines you will find the first line therapies, second line therapies, and typically the therapies with the best evidence are the non-drug treatments. This slide just shows non-pharmacologic approaches to managing chronic musculoskeletal pain that were determined really to be ready for broader use recommended for broad rollout in VA, according to a State of the Art Conference held a couple of years ago. And there’s a citation at the bottom if you want to learn more about that. This and other related articles from that SOTA were published in the Journal of General Internal Medicine, a special edition in 2018.

So, I’ll wrap it up after giving credit and thanks to a lot of other people who were involved. You know, I have the glory and the glamour of getting this best paper award, but I really do have to thank and credit our Veteran participants who were so devoted to this study, my primary care colleagues who were willing trust me with recruiting their patients for this study, and then all the other best paper coauthors, clinicians who worked on SPACE and other SPACE research team members who contributed to this effort. And I’ve left, I think, about 15 minutes for questions. So I look forward to more conversation. Thank you.

Molly: Thank you so much, we have several pending questions, and for those of you that joined us after the top of the hour, to submit your question and comment please use the GoToWebinar control panel located on the right-hand side of your screen. Down towards the bottom there’s a question section, just click the arrow next to the word questions, that will expand the dialogue box and you can submit them there. So we’re just going to jump right into them. Did you exclude patients with chronic migraine?

Dr. Erin Krebs: Aha, yes in fact we did. So there were two types of pain patients who we excluded, and they were the two conditions that we, you know, we had some prescribing-existing evidence that opioids could worsen those conditions. One was frequent chronic migraine and the other was fibromyalgia. So if patients had a diagnosis of fibromyalgia or they had frequent chronic migraine headaches we did not include them in this study.

Molly: Thank you. The next question, just wondering if you have any info on patients with migraines and how they did with the opioids? But it sounds like you did not include them, so we can move on.

Dr. Erin Krebs: Yeah, we did not include them and, you know, my understanding is really migraine guidelines, the American Academy of Neurology and others have looked at this and really it looks like opioids harm these folks and so we were, we certainly didn’t want to include people who had a pain condition that would be likely to be worsened.

Molly: Thank you. The next question, I wonder if they compared treatment preference with assignment to see if that was balanced or not?

Dr. Erin Krebs: Ah, so indeed we did, and it’s a little complex. So let me see if I can pull that out here. So, what we found is that there was a slight imbalance in that, all right, so patients who preferred the opioid group were a little bit more likely to end up in the nonopioid group. And, you know, what that suggests is, so you know, the concern here, of course, is bias, right? That patients’ preferences may bias their outcomes, so you know, in general patients in the study thought opioid work better. So that’s sort of a preference that might bias us towards a finding in favor of opioids. Likewise, this slight imbalance here where more patients who preferred opioids ended up assigned to nonopioids, that also would tend to bias in favor of the opioid group. So it would have really been a big problem if opioids had been slightly superior. But given that opioids were not superior, and these biases probably favored opioids we’re, actually we’re pretty reassured by that.

Molly: Thank you. The questions are pouring in. Why was opioid dosage limited to a hundred MME?

Dr. Erin Krebs: Ah, good question. So, one thing that was interesting about doing this study at the time that we did the study is that the world changed a lot over the course of the study. So, you know, I was originally writing this proposal back in 2010, before all of these papers came out looking at opioids, and dose-dependent, risk of overdose, death, and other serious harms. That started to happen around 2011 and 2012, and so concern was heightening around the time that we actually started enrolling patients about overdose risk and death risk. So, when I originally wrote the proposal the dose, upper dose limit was 200 morphine equivalents. And to be totally honest, we just got cold feet. So by the time we started it we changed that upper dose limit, so you know, basically between the proposal and the start of recruitment we reduced the upper dose threshold to a hundred morphine equivalents. I was just concerned about causing deaths, since I was not exercising any clinical judgment in terms of who was going to get opioids here, I was letting the computer drive. I was a little more nervous, I was nervous. I should say that because of this really careful trial approach that we used with each individual patient, so a patient in the opioid arm we would start them on something and gradually increase their dose. If they got to a point where a dose increase did not improve pain or led to side effects, we would just back off. And so we did not see the kind of dose escalations that you see in practice, I think. Because most patients in the study they, you know, the point where they got the sort of best individual balance of benefit to side effects was a relatively low dose. So, you know, patients we would bring them up and then bring them down trying to find the sweet spot in terms of where they got the best personal effects. And in this study really only a small number of patients required a dose over 50 morphine equivalents to achieve that sort of individual best balance point for them. So I actually don’t think the, it probably mattered much that we had lowered our top dose from 200 to 100.

Molly: Thank you. Do you support the use of opioids for use in severe acute pain, and if so, how long do you general endorse it?

Dr. Erin Krebs: Well, you know, much like chronic pain, acute pain is a pretty diverse set of issues, and actually I would say acute pain is even more diverse on some level because with acute pain really the pain is often reflecting whatever the underlying issue is. So, you know, if you’re talking about post-operative pain, you know, you may have mild or short-term, very short-term pain with a, like a tooth extraction, or much more severe and prolonged pain with a knee replacement so, or abdominal surgery, so I would say it’s impossible and shouldn’t be tried to make generalizations about acute pain. I should say that in terms of the conditions, you know, the common conditions we see in primary care and urgent care settings, you know, like acute back pain or acute joint pain. There have been a couple of recent trials that have similarly found that opioids are not better than nonopioids. So, just the last couple years a couple of studies conducted in the emergency department that were very pragmatic, you know, enrolled, one of them enrolled patients who were presenting with, you know, acute back pain, randomized them to opioid versus just NSAID. You know, and really adding opioids did not, it did not improve outcomes. Similarly, another study enrolled patients who were presenting with acute extremity pain, and they used a really pragmatic definition looking at pain that was severe enough to indicate the need for some kind of imaging study, you know, to rule out fracture or some kind of trauma. And they likewise randomized patients to Nonsteroidal Anti-Inflammatory or opioid and, again, opioid not having any incremental advantage. So, it seems like for the most common acute musculoskeletal pain presentations that opioids are probably not valuable for most patients who could take other options, yeah.

Molly: Thank you. The next question we have, how did you define, quote, chronic back pain? Idiopathic, failed back surgery, et cetera?

Dr. Erin Krebs: So, we used a pragmatic definition here, again, we talked about the duration and that it was, you know, located in the back and that it was moderate to severe in nature despite other medications. So we did not, you know, look at whether they had, for inclusion purposes we didn’t look at whether they had surgery or that kind of thing. We did ask about that, and actually a large number of patients in the study had had spine surgery, so it was a pretty, it was a group that had had chronic back pain for many, many years, most of them, and many of them had had a whole wide range of interventions over time.

Molly: Thank you. Let’s see, did any SPACE patients undergo surgical procedures, hip or knee replacements, spine surgery?

Dr. Erin Krebs: Yes, so both before and after this, or I’m sorry, before and during the study we did have patients who underwent surgeries. I actually don’t have this right in front of me, but I published this in the main JAMA paper, if you go to the JAMA website, and I think at this point it’s open access, so everyone should be able to get to this. If you go to that main paper there’s a supplement section, and there’s a whole bunch of supplement tables, including tables that look at, that describe the patient-reported numbers with spine and joint surgeries, both at baseline, so prior to the trial, and at 12 months, so over the course of the trial.

Molly: Thank you.

Dr. Erin Krebs: I should say, we asked patients, you know, in the beginning. We did exclude patients who had planned surgery in the 12 months of the study. So if somebody knew they were going to have a joint replacement, for example, we didn’t enroll them, but if they ended up having a joint replacement that hadn’t been planned prior to enrollment, we didn’t exclude them, we kept everybody in, in an attempt to treat approach.

Molly: Thank you. The next question, were non-pharmacologic therapies allowed to complement the two prescribing strategies? Were they encouraged? Is there data on use of these therapies among patients in the trial?

Dr. Erin Krebs: So, yes. We made no attempt to restrict use of non-medication therapies. So, you know also, I mean talk about the world changing during the course of this study. Our VA medical center established additional pain, non-drug pain treatment options and, you know, there’s been a lot of activity in that area clinically over the past five to 10 years. So a lot of patients did try other things and we didn’t, you know, we didn’t promote it in an organized fashion, but we generally did, you know, encourage people to do what they, you know, if their primary doctor was recommending something we supported that. So we did not want people to be deprived of other appropriate options. We tried to get patients not to take medications for pain, other than those we were prescribing, but for non-drug therapies, they were free to use what they wanted, and what we did is we just asked, you know, we asked at baseline, we asked at 12 months what they had used, and those data are also reported in that supplement table section on the JAMA website.

Molly: Thank you, we have had people asking for the reference to your paper and to other citations you’ve mentioned. So I’ve been giving people the reference to the page about your paper, which leads to everything, so I hope that’s an okay solution.

Dr. Erin Krebs: Great. And as far as those acute pain trials, you know, I could, I could send those out later too.

Molly: Yeah, I also told people they can contact you offline. Sorry about that, [unintelligible 59:24]

Dr. Erin Krebs: There you go. You can see my email on the lower right-hand corner there.

Molly: Exactly. Exactly. Okay, so the next question, in terms of billing and coding there’s a debate in the industry when it comes to prescribing opioids and toxicity. From a provider point of view do you consider these patients and their presenting problems high risk or moderate risk?

Dr. Erin Krebs: Well, I guess I’m not sure what the question is, so I guess risks for what? Would be the\_

Molly: [unintelligible 1:00:00]

Dr. Erin Krebs: I mean I think we know that opioids are high risk medications.

Molly: We can have them write in with further clarification while we move into the next\_

Dr. Erin Krebs: Sounds great.

Molly: \_one. Okay.

Dr. Erin Krebs: Sounds great.

Molly: Do you feel there, oh so to our question submitter please write in for further clarification. Do you feel there are limitations and biases based on the recruited population, our Veteran patients, compared to opioid efficacy conducted among general populations? What are the limitations and biases, if you think there are any?

Dr. Erin Krebs: So, of course, every study has limitations. You know, we do our absolute best to address them and to prevent bias, but you know, there’s no perfection there of course. So I should say that all trials as a limitation, you know, patients who enroll in trials are probably different than patients who don’t, right? So we can look at characteristics of our patients compared to, you know, what we know about VA patients with chronic pain or VA patients on opioids. And, you know, in general our patients enrolling in this study looked similar, but you know, the unmeasured things are what we don’t know. So, you know, many people would just not join a trial and trial joiners are probably different. I think a big limitation of the study, of course, is that we couldn’t blind patients or clinicians. Our primary outcomes were patient-reported, so really, we were concerned about bias, in particular, that would favor opioids in this study, and I think likely that’s the direction of most biases that would affect the study. So the benefits of opioids may have been inflated here. You know, that there was this imbalance in the pre-randomization treatment preference, that again probably favored opioids, because more people who wanted opioids ended up in the nonopioid group. You know, another thing about this study in VA particular, you know, is that we had only 13% women. We really, you know, we tried to get as many women as we could, and I feel like we did a pretty good job considering VA, but if we did this in a non-VA setting, likely 60% of the patients would be female and it would be a minority who were male. In the supplement, I already mentioned we did report our findings according to male versus female. And, you know, really looked like the women that had, you know, better response to the nonopioid group than the opioid group, and that was kind of a more pronounced thing than among the men. Statistically we just simply don’t have power. So it’s kind of hypothesis generating I would say that, you know, maybe nonopioids are better than opioids for women, but we can’t say that. We’re just limited in our ability. And then, you know, another big limitation I mentioned already, and I like to say all the time is, you know, these results really don’t apply to people who already have physical dependence to opioids because they’ve been on long-term opioid therapy. I’m sure we could come up with many more.

Molly: Thank you. We do have about half a dozen pending questions, but we have reached the top of the hour. So I’m going to ask two things. One, are you able to stay on and answer a few more questions so we can capture them in the recording?

Dr. Erin Krebs: I can stay on, yes, for a few more minutes.

Molly: Okay, sounds good. So for those of you that either need to sign off now or your question does not get answered on the call feel free to follow up with Dr. Krebs. If you do need to sign off, please wait just a moment while the feedback survey populates on your screen. It’s just a few questions, but we would like to get your feedback on today’s presentation and the program as a whole. So thank you. Okay, so we did get some clarification about the previous question, so again, I’ll repeat it. In terms of billing and coding, there’s a debate in the industry when it comes to prescribing opioids and toxicity. So this is in terms of toxicity from a provider point of view, do you consider these patients and their presenting problems high risk or moderate risk with regard to toxicity?

Dr. Erin Krebs: So I would say that opioids are high risk drugs in terms of toxicity, you know, much like we would say warfarin and insulin are high risk drugs in terms of toxicity. You know, I think there are patient factors and there are treatment factors that may increase the risk, but it’s clear that adverse outcomes, you know, especially death occur in people prescribed opioids at all doses and all types of people. So I mean, I guess I would consider just across the board that it’s the drug that is the high risk thing. I hope that answers the question.

Molly: Thank you. Given the apparent effectiveness of utilizing a collaborative team-based treatment model with more frequent visits by the pharmacist care manager, are there any plans regarding studying implementation of this model/rollout of the model VA wide?

Dr. Erin Krebs: So, I don’t know if the person who submitted that question knows this or not, you know, if yes, hey thanks for setting me up, if not, I guess thanks for setting me up. So we do have a trial currently funded by PCORI, the Patient-Centered Outcomes Research Institute, and supported with VA resources and time that is ongoing now at nine different VA facilities. And it’s comparing this model, this pretty straight forward Telecare collaborative management model to a more intensive interdisciplinary pain team treatment model for patients who have chronic pain and long-term opioid use. So, in that particular study, it’s really focusing on both opioid dose reduction and intensification or improvement of nonopioid treatments. So, that is recruiting, ongoing now, and it’s called the VOICE trial, and I think let’s see, we currently have a website up and running. It is www.voice.umn.edu I believe.

Molly: Thank you. So I will read another question or two and you can just let me know when you need to hop off. For participants taking acetaminophen was there concern for liver damage?

Dr. Erin Krebs: Yes, so I mentioned that we enrolled all kinds of people. So in this study, there were many patients who had medical problems, other medications that could cause drug interactions, other health problems that might be a problem with any number of the medication options that were included in this study. So, patients in terms of their treatment it was really individualized based on what their situation was. We did limit acetaminophen dosing to a lower level of dosing for people who we thought might have a higher risk for liver problem. There were some patients who, for example, would not be candidates for Nonsteroidal Anti-Inflammatories at all because of, you know recent coronary event, or you know renal, chronic renal disease. There were quite a few people who had some serious contraindications or issues with specific drugs, and you know, so a lot of the people in the study were not able to try all of the drugs on the, you know, in their prescribing strategy. They may have had very few options on the list, but everyone had at least some options. We ended up using quite a few topicals for this reason. We had a lot of elderly patients who didn’t tolerate medicines well or who had contraindications, so that’s probably why we used so much topical lidocaine, we used, you know, topical capsaicin as well, and then it was only in the last six or nine months of the study that topical diclofenac was added to the VA formulary. And so once that was on the VA formulary, we used that too.

Molly: Thank you. So I’m going to ask the four people that submitted the remaining questions to contact you offline to get responses. I do want to wrap things up, I want to give you the opportunity to make any concluding comments that you’d like to, to the audience.

Dr. Erin Krebs: Well I just, I thank you for your attention and thanks for sticking with me here 10 minutes after the hour. And, you know, I’m happy to answer questions by email or send any of the resources that, or citations that I mentioned. So please just feel free to shoot me an email. And, you know, it is possible I might get back to you after my next proposal submission deadline next week, but I will get back to you. All right, thank you.

Molly: Thank you so much, Dr. Krebs, for this informative presentation and congratulations again on the prestigious award. And thank you to our attendees for joining us. At this time I am going to close out the session, so please wait just a second while the feedback survey populates on your screen. Thank you, everyone, for joining us and have a great rest of the day. Thank you, Erin.

[ END OF AUDIO ]