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Session: How Have National Reductions in Opioid Prescribing in the Past Decade Impacted the Health Outcomes of Veterans Experiencing Chronic Pain?

Presenter: Evan Carey, PhD

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Heidi Schlueter: Hi, everyone. This is Heidi Schlueter at CIDER, and I want to welcome you to today’s HSR&D Cyberseminar. Today’s session is a part of our Spotlight on Pain Management Cyberseminar series, and today’s session, “How Have National Reductions in Opioid Prescribing in the Past Decade Impacted the Health Outcomes of Veterans Experiencing Chronic Pain?” We’ll be getting started in just a moment here. Just a couple quick things to go through before we get started. If you did not see my email that I sent out, today’s session is accredited for physicians, nurses, physician assistants, social workers, and psychologists. If you do want CME or CEU credit, please register and access the session through TMS or TRAIN; TMS for VA employees, TRAIN for non-VA attendees. You’ll be able to access credit using those portals. There was a link included in the reminder that was sent out this morning that should help you out with that.

If anyone is looking for handouts or captions for today’s session, we do have those available. There are tiny URLs that will be on your screen in just a moment. You would need to type those into your browser window, or again, they were included in the reminder that was sent out for direct clickable links or will be up on your screen in just a moment.

If you do have any questions that come up during today’s session, please use that Q&A portal in GoToWebinar to submit those questions in to us. We will have time for questions at the end of today’s session.

Since we’re just past the top of the hour here, we’ll go ahead and get things started. Robin, can I turn things over to you?

Dr. Robin Masheb: Thank you, Heidi. Good morning, everyone, and welcome to today’s seminar, Cyberseminar, and kickoff to the 2018-19 academic year for Spotlight on Pain Management. Exciting news for this year is that we have made this seminar eligible for continuing ed credit for most professionals. This is Dr. Robin Masheb, Director of Education at the PRIME Center of Innovation at VA Connecticut, and I will be hosting our monthly pain call entitled Spotlight on Pain Management. I apologize for my voice today, but I have a case of laryngitis.

Today’s session is “How Have National Reductions in Opioid Prescribing Impacted the Health Outcomes of Veterans Experiencing Chronic Pain?” I would like to introduce our presenter for today, Dr. Evan Carey. Dr. Carey has a Master of Science in Applied Biostatistics and a PhD in Epidemiology. Dr. Carey is an assistant professor at the Saint Louis University Center for Health Outcomes Research. He is also a data scientist with the Denver-Seattle Center of Innovation. His research interests include studying national trends in chronic pain and related treatments as well as access to health resources for rural Veterans. Our presenter will be speaking for approximately 45 minutes and will be taking your questions at the end of the talk. Please feel free to send them in using the question panel on your screen.

If anyone is interested in downloading the slides from today, please go to the reminder email you received this morning, and you will be able to find the link to the presentation. Immediately following today session, you will receive a very brief feedback form. We appreciate if you complete this as it is critically important to help us provide you with great programming.

Dr. Friedhelm Sandbrink will be joining us today. He is a neurologist, the VA Acting National Program Director for Pain Management, and Director of Pain Management in the Department of Neurology of Washington, D.C., VA Medical Center. He will be taking questions related to policy at the end of our session.

And now I’m going to turn this over to our presenter, Dr. Carey.

Dr. Evan Carey: Thank you so much, Robin, and thank you all for joining me today. I greatly appreciate it. It’s a wonderful introduction. Look forward to questions at the end of the talk.

So as mentioned, today we’re here to talk about how national reductions in opioid prescribing in the past decade in the VA have impacted health outcomes of Veterans, and so we’re seeking to answer that question.

I’d like to start with some acknowledgments. First of all, I must thank the Denver-Seattle COIN, VA COIN, for supporting this work and supporting me for so many years. Also the collaborators of course. I could not have done this without them. Dr. Joe Frank and Bob Kerns, Gary Grunwald, Mike Ho. Friedhelm is on the call as well. And the entire Denver/Seattle analytic team has, so helpful to go back and forth with work.

All right, so let’s talk a little bit about an outline of what we’re going to go through in the next 45 minutes. So I promise we’re not going to get too mathematical, and I’m going to try to keep this not too technical. But we will start to think a bit about what are the different methods that are appropriate for using observational data like a national pain cohort to answer policy questions of interest. So we will have to scrape that a bit, but we’ll introduce it gently.

We’ll start with a history of policy and opioid prescribing in the VA briefly, review some trends that have been published in the prevalence of chronic pain and related treatments for chronic pain. We’ll talk about the populations of interest that actually might be affected by these changes, national changes in opioid prescribing, and then go on to think about what negative health outcomes might be associated with exposure to long-term opioid therapy.

From there, we want to move into really specifically thinking about a research question to include the population. We want to answer the question then, and the exact exposure and outcomes. Talk about methodologically how can we make fair comparisons between an exposed and an unexposed group when we don’t have a clinical trial to control the exposure. I’ll review the methods for this particular study and go through the results and talk about some discussions and implications and next steps.

So this is a little bit of a case study in addition to a presentation of results for a research project I’ve been working on well over a year now. So let’s start with a clinical background of chronic pain opioid prescribing in the VA. I think everybody on this call realizes chronic pain is important to study. It is a leading public health issue in the VA and in the private sector. In fact, a large number of people, and Veterans in particular, are at an increased risk of chronic pain.

Throughout this presentation I’d like to highlight a number of different VA-affiliated researchers who have done excellent work in this space. So we’ll start here that through, survey study essentially found that Veterans reporting severe pain 9.1% of the time compared to non-Veterans at 6.4%.

So not only is chronic pain, or in this case severe pain, prevalent, but it’s especially pertinent within the VA. In general, in the United States opioid prescribing has decreased. There’s really a wide variety of studies and sources you can cite to kind of look at general opioid trends over the past 10 years. I’ve chosen to review a study recently published by Dr. Bohnert, who is a VA researcher as well, VA-affiliated researcher. This was national estimates of overall opioid prescribing as well as high-dosage opioid prescriptions and the rate of benzodiazepine co-prescribing. And in this study, she noted the national estimates were generally decreasing between 2012 and 2017. In particular, she noted that the timing of some CDC guidelines released in March of 2016 were associated with a steeper decrease, sort of an interrupted time series analysis.

But certainly nationally, opioid prescribing has been decreasing. And I’d actually, I’d like to make the argument that really the VA has led the way when it comes to national reductions in opioid prescribing. I don’t think that’s a very controversial statement to make. A recent editorial published in 2017 detailed really nicely a variety of programs the VA has implemented over the past, I suppose, nine years there that we would presume directly affect opioid prescribing.

We start in 2009 with the stepped pain treatment policy directive, with an expansion of complementary and alternative medicine and access to non-opioid pharmacotherapy. In 2010, we had some opioid therapy guideline adherence metrics started with some sort of audit and feedback mechanisms to facilities in terms of implementation of those guidelines. In 2011, the SCAN-ECHO pain management was started and continues to be active to this day where specialists in pain medicine connect with primary care and mid-level providers to help train them on caring for Veterans with chronic pain. Then all the way into 2013, we’ve got the opioid safety initiative, state prescription drug monitoring, and so forth.

So without reviewing those all in too much detail, we can certainly see that there’s been a very regular effort by the VA to address both chronic pain care generally and quite specifically opioid prescribing.

So what affects has that had? From the same review, there’s some figures presented. This is from 2003 to 2017, so a pretty long range, longer than we’re going to be looking at later in this study, and generally noted that the number of Veterans dispensed at least one opioid medication did increase up until 2011 or ‘12 and then plateaued and has decreased substantially since then. But high-dose prescribing as well as concurrent opioid and benzodiazepine prescriptions have generally been decreasing throughout this timeframe.

So continuing on with that trend, I’ll review a little bit of work that actually I published and completed just this past spring. We isolated an incident chronic pain cohort, Veterans newly reporting chronic pain, and we studied just temporal trends in those opioid and non-opioid treatments. That was just published this spring. But essentially what we found is that a variety of non-opioid treatments, both non-opioid pharmacotherapy as well as non-pharmacologic treatments, were generally stable or increasing in prevalence amongst this incident chronic pain population and that any opioid as well as long-term opioid therapy exposure was generally decreasing at the same time. I believe this was over one year subsequent to baseline, so you’ll note in 2010 was about 20, a little under 25% all the way down to 10% by 2015.

So certainly there has been a substantial amount of policy at the VA in the past 10 years, directed at decreasing opioid prescribing, in particular directed at decreasing long-term opioid therapy for chronic pain. We see that there has been a really large number of increases that might be sort of correlated in time with that. It’s really actually quite hard to disentangle that and to say exactly which one of those efforts really caused the decrease. I suspect it was kind of joint cumulative effect of all of those various national efforts, including ones I failed to list on that slide.

So I think a really reasonable next question from there is to think about what did those reductions get us in terms of Veteran health outcomes? So I want to mention the SPACE clinical trial that was very recently published by yet another outstanding VA-affiliated researcher, Dr. Erin Krebs. Essentially she found that this was a clinical trial where they randomized opioid and non-opioid-assisted therapy, 240 Veterans. And the main findings were that the opioid-assisted therapy amongst these Veterans reporting chronic pain was not superior to non-opioid-assisted therapy. Similar outcomes, and I think there was one outcome and it was possibly favorable to the non-opioid group, and there was some patient reported medication-related symptoms, I believe, that showed a negative effect within the opioid group. But all the broader adverse outcomes that they analyzed, they did not find a significant difference in that initial published paper between those two groups.

So my take-home from that paper was that opioid therapy is not effective per this clinical trial for chronic pain amongst this population. However, what the clinical trial didn’t tell me was what effect does opioid therapy potentially have on negative health outcomes? I suspect the effects are modest and you just need a lot more power to detect that.

So of course we’re not going to have another clinical trial like this, and I don’t think we’ll have an answer to that question from a clinical trial where we might expose a couple thousand Veterans to opioid therapy and a couple thousand not just to see what the potential negative outcomes are. Right? That’s certainly not going to happen. So really what we’re left with is trying to leverage the observational data we have from this past 10 years of large variation, mostly decreasing variation, in opioid prescribing to try to understand what sort of effect opioid prescribing, long-term opioid prescribing, has had on this population on health outcomes.

All right, so a bit of a history of the clinical backgrounds. Let’s now think about negative outcomes potentially associated with long-term opioid therapy. I specifically say potentially associated because there’s actually not a lot of support in the literature for specific outcomes. Right? So we have observational studies sort of here and there that have found relationships with outcomes. But generally the quality of that evidence has been graded to be average or less.

So I mentioned a review, systematic review, at the bottom that has a bit more details about some of these from 2015. I believe there is an updated one coming out shortly. But some of the hypothesized negative health outcomes are falls and fractures; substance use disorder, both opioid and non-opioid; sleep disorders; hyperalgesia. Mortality has generally been proposed, though I think the pathway is a bit unclear, although we can easily measure mortality, so it’s always an important outcome to look at. Certainly some of these other things could lead to an increase in mortality. New incidents of depression, and there was one medium-sized observational study that found a link with cardiovascular risk. These are potential outcomes that might be associated with long-term opioid therapy. We’ve got some references at the bottom that you can review.

All right. So we’ve got this idea that there has clearly been a lot of movement in opioid prescribing in the VA over the past 10 years. And furthermore, there’s identified outcomes that may be affiliated with opioid prescribing. But one thing we really need to think about to clearly define our research question is what population do we expect to actually be affected by changes in VHA opioid prescribing?

So we could think broadly at first, just the general U.S. population. The VA is a huge provider of care in the United States, and at one time, a large supplier of opioids depending on the prescribing practice. So certainly in the context of diversion of prescription opioids, there is probably a broader health effect in the U.S. population of decreasing the supply of opioids sort of put out there by the VA. However, that’s quite hard to measure and that’s not a focus of this study. But it’s important to note that that is a population health benefit likely from these trends. However, we won't be quantifying that today.

If we focus in on Veterans actively engaged in primary care in the VA, the Veterans that we take care of, there’s possibly a benefit to those Veterans, the decrease in opioid prescribing. However, I would think that benefit would be focused on Veterans in chronic pain as the primary indication for long-term opioid therapy would be chronic pain, and certainly in the mid-2000s to the late 2000s that would be the primary indication.

So if we focus in on this group of Veterans reporting chronic pain that are going to be affected by these changes in opioid prescribing, there’s really, I think, at least three subsets that I think would be affected by these changes. One subset would be those currently on long-term opioid therapy, so Veterans that have been on long-term opioid therapy, perhaps for quite a while. And they’re now being asked to discontinue long-term opioid therapy as a function of these broader changes in opioid prescribing in the VA. We’re not going to be studying them today, but I do want to mention them as an important subgroup, and that will be a next step I’ll identify towards the end.

There’s also the idea of the prevalent chronic pain group; that’s Veterans that have been experiencing chronic pain for quite some time. And then I separate this out. It’s a bit of a construct that I’ve come up with, and it’s Veterans newly reporting chronic pain, and I call them the incidents chronic pain group. It would be Veterans that are actively in primary care in the VA and have not previously reported chronic pain and newly report it to the VA. This could be a longstanding condition that could just be new to the VA, or it could be a new condition that has just come up for them recently. We call them the incident chronic pain group, or perhaps more appropriately, the newly reporting chronic pain group.

So all of these groups are important and all of these groups are likely affected by changes in VA opioid prescribing. However, we’re going to focus on that incidents chronic pain group for the results in this presentation.

All right, so we’ve got this idea, this newly reporting chronic pain group of Veterans, and we’ve had a large decrease in long-term opioid therapy prescribing in the VA over 10 years. And we’ve observed their outcomes over the past 10 years. So we know we can't do a clinical trial to mimic this. We’re not going to randomize several thousand Veterans to opioid therapy and several thousand to non-opioid therapy just to see what negative outcomes might happen. Right? That would not be ethical. Certainly never going to happen. But the question becomes can we use this national observational dataset of all of these Veterans and their health outcomes to identify causal relationships? The sort of things we would identify in a clinical trial. And that’s really what this presentation is going to be focused on, the idea of doing that.

So whenever we’re trying to do work like this, I think it’s really appropriate to first start by thinking about what are the comparisons we really want to make. And actually from a clinical perspective, who are the Veterans I’m comparing here? So we’ve got this general idea that long-term opioid therapy exposure might be related to some bad outcome. I’ll list out some outcomes later that we’ll be looking at.

So I think what we might think of is there’s a Veteran in 2008 newly reporting chronic pain and they are one of that 20 or 25% who is exposed to long-term opioid therapy. But what if this same Veteran was not exposed to long-term opioid therapy? What would the average effect on their outcomes have been? Right? That the kind of question we go after in a clinical trial, and that’s what we’re going to try to go after with this observational dataset.

So if we simply compared the outcomes of these Veterans exposed to long-term opioid therapy versus those unexposed, would that be accurate? Right? That’s a challenge. So that’s the first step we’ll take. We’ll just say who was exposed, who was unexposed, and what was their difference in outcomes? But there’s a problem with doing that. Right? I suspect some of you know what that is. The issue is that Veterans who receive long-term opioid therapy are different from Veterans who do not receive long-term opioid therapy for a variety of reasons. Right? It could be sort of an indicator of overall things not going well for reasons other than the opioid therapy.

So really the idea is that can we somehow find a Veteran, maybe in 2008, who was exposed to long-term opioid therapy, and can we find another Veteran in 2016 who looks just like that Veteran in 2008, very similar clinical profiles, similar everything that we can observe, except they were not exposed to long-term opioid therapy because of all these policy changes and decreases in opioid prescribing? That’s kind of what we’re going after with this sort of study design, which we’ll get into a bit more later.

So of course the issue with simply comparing these outcomes is that they may be different for reasons other than exposure, and we call those confounders. Right? Anybody who has taken some epidemiologic coursework, this is probably a bit of review. But some examples are that Veterans who report really intense pain may be more likely to receive long-term opioid therapy. Veterans who have tried multiple non-opioid alternatives outside the VA may be more likely to receive long-term opioid therapy sort of as a last resort. However, I might not observe those things. So I can observe the pain scores if they came to the VA, but I can't observe all of the yoga they’ve tried and the things they’ve tried outside of the VA if it’s not in our administrative data. So the problem is these confounders may or may not be observable. That’s the root issue in these sorts of analyses.

There’s a couple of different sort of modern approaches we can take. And I say modern. I’m actually going to stick with what I consider to be modern/traditional approaches. One would be direct regression adjustment. This is essentially where we fit a multivariate model, you sort of, what we would call adjust for the confounders that we can measure. We’re basically attacking that relationship right there, that X, to say if we remove that relationship, what we’re left with is the effect of long-term opioid therapy on our bad outcome. So examples of that would be like linear or logistic regression, and that’s probably something you’ve learned about before. And we’ll implement that on this dataset.

Another potential approach is to attack the other side of this little triangle. Instead of conditioning out the relationship between the confounders and the bad outcome, we can try to balance based on observed differences. So the strategy I mentioned earlier, this idea that there is some Veteran who looks very similar to another Veteran except they didn’t happen to get exposed to opioid therapy, but they’re the same age. They’re the same gender. They have the same clinical profile. They have the same mean pain scores in the 90 days prior to baseline, that sort of thing. But one of them got opioids and one of them didn’t. That’s the sort of thing we might be able to leverage.

One way to do that is via propensity score analysis where we model the probability of exposure using these confounders and essentially create a synthetic sample where the treatment groups are balanced based on that exposure model. We’ll see later what I chose to implement is something called inverse probability of treatment weights. However, there’s a few other options, and we’ll see actually that they didn’t behave that well, so we’ll probably need to implement some more to really disentangle it.

There’s some references there if you’re unfamiliar with these methods that you could certainly review. They’re quite approachable.

All right, sort of the final touch. We think of direct regression adjustment. We think of propensity score. Just general balancing based on observed covariate approaches, something called instrumental variable analysis. The idea here is that if we can find something that is causing variation in opioid prescribing, maybe we can use it. What are the things that might cause variation in opioid prescribing?

Well, we might find that some facilities are much more likely to prescribe opioids than other facilities. That would be a potential instrument, and we could compare the Veterans at one facility of the high-prescribing facility versus the Veterans at the low-prescribing facility and see if they have different health outcomes. Another option might just be calendar year. We’ve seen a large difference between 2008 and 2016 in opioid prescribing. So maybe we compare the outcomes of the Veterans in 2008 compared to those in 2016, and the idea is that the calendar year is sort of the instrument.

I’m not going to go through the results for this analysis. It turns out that it’s really hard to find valid instruments, and I’ve done this a couple of times. I did not have success finding a valid instrument for both prescribing preference or calendar year in this cohort. But certainly if we’re thinking of kind of the big three methods for doing this sort of work in observational data, this would be one of them, so I do bring it up.

All right, so let’s move on to our actual research question’s specific aims. We’ve got a bit of methodologic background. We have a bit of clinical background. Among Veterans newly reporting chronic pain between 2008 and 2016 who are actively engaged in primary care is my incident chronic pain group. How has exposure to long-term opioid therapy changed? So this is exposure to long-term opioid therapy within six months. Our hypothesis would be that long-term opioid therapy exposure has really decreased over this time period, which of course, we’ve seen that in the data already. But we’ll see it again in this dataset.

Then in the same token, okay, we’ve got the opioid therapy decreasing. In this same cohort, has the probability of negative health outcomes changed substantially? We’ll see that I chose to do mortality as well as ED and inpatient utilization for a couple of difference outcomes, and we looked for them over two years. So a Veteran reports chronic pain, and then within two years they are, well, within one quarter they’re exposed to long-term opioid therapy, and then within two years do they have this bad outcome?

So then finally, in this cohort, is there a causal relationship between that long-term opioid therapy exposure and the negative health outcomes? Our hypothesis is that yes, there is an increased risk of these negative health outcomes.

So we’re not going to present this work. The methods briefly, the analytic approach, and I’m going to go through these pretty quick so we can focus our time on the results. But I wanted to identify all Veterans engaged in primary care. This is a national cohort. It’s not a sample. So we used CDW, used the full medical record of every Veteran engaged in primary care, really from 2006 to 2016, with the analytic timeframe being 2008 to 2016.

We discretized time into year-quarters. Actually gets really hard to work in large data when you leave time continuous. So instead of thinking of exact number of days to an outcome, we tend to think of time in year quarters in this study, so each calendar year broken into four quarters.

At the start of every one of those year quarters, we identified if the Veteran was reporting chronic pain in the current quarter or the prior four quarters. We identified chronic pain based on patterns of elevated pain scores at least 30 days apart but no more than one year apart, as well as occurrence of conditions related to chronic pain. Have a list of those later in appendix, and you can certainly email me. We can provide a more detailed list. Those did have to occur twice over at least 90 days, the chronic pain conditions.

Newly reporting chronic pain is that first quarter where a Veteran meets criteria. So we did do a washout from 2006 to 2008 so that if a Veteran reported chronic pain in 2006 or 2007 they would not be included in this cohort. We also identified a number of active chronic illnesses based on ICD-9 and 10 codes in the prior four quarters or current quarter and then a series of demographics for each Veteran as well as some pain scores.

Our data source was the VA administrative data, the CDW. There’s some details about that there. But I’ll go ahead and skip through that.

I want to talk a little bit more about this study design because I think it is a little bit to wrap our heads around, although I did make it really simple as possible, still respecting the complexities of the situation. So we discretized time into these calendar year quarters. Really, our analytic cohort is going to be active primary care and incident chronic pain from 2008 and actually to the end of 2016. If over two years passed since their last primary care visits or if the date of death was reported, we would censor them from the analysis. Then we calculated all of the other variables that we mentioned.

I did exclude Veterans missing their home primary care station as well as those whose care station was not a clinic or a VA medical center. That was in support of the instrumental variable analysis, although it ended up being a relatively small number of Veterans.

All right, so the study design. To give you a bit of a visual, the idea is that at some point a Veteran newly reports chronic pain to the VA, either from pain scores or from patterns of ICD-9, ICD-10 diagnoses likely to be related to chronic pain. We looked backward and in that current quarter to say, well, what is their comorbidity profile at baseline? Do they have cancer? Do they have diagnoses for heart disease? Do they have diagnoses for pulmonary disease or depression? A number of different comorbidities were identified.

We then look forward in the current quarter and the next quarter to identify exposure to long-term opioid therapy. Then in quarters three through eight over that next, really, about two years out, we looked for the outcomes. By definition in the study design, they had to be eligible at least two quarters in the cohort, so they would not have had a date of death prior to that point. So we’re really looking at outcomes, including mortality, over two years, but it’s really a year, kind of quarter three through eight there.

But the interpretation then becomes we have a Veteran newly reporting incident chronic pain. Do they initiate long-term opioid therapy? And if they do, what is the association with negative health outcomes within two years?

All right, so a bit about the negative health outcomes that we looked at. What we would love to look at is impact on quality of life, function, interference. Right? But we don’t have those things readily available in the electronic medical record, so those are things I cannot look at in this study. However, what we can look at is mortality. We have pretty good mortality data in the VA. Then we can look at emergency department or inpatient utilization for specific diagnostic codes. So that’s what I chose to do. So we’ll report all of these outcomes in the study: Mortality within eight quarters; sort of a combined suicide, suicidal ideation, and self-injury; also falls, fractures, traumatic joint sprains and strains I combined into one category as well; substance use disorder, opioid; and then all other substance use disorders. Then we added a falsification outcome.

So a big problem, potential problem of doing work like this is that you will identify a range of negative health outcomes and you might find that your exposure is related to all of them. And it might be that your exposure suffers from something called treatment indication bias. And it’s that idea that Veterans who are exposed to long-term opioid therapy, they’re just not the same as the Veterans who were unexposed, who didn’t get long-term opioid therapy, and they’re not as healthy. So they’re going to have more of all of these things. And it’s not the opioids causing it. It’s just the opioids are kind of a flag for this state of being unwell that leads to these outcomes. That’s called treatment indication bias. And it’s really a large problem that we’re constantly trying to overcome in observational studies.

One way to possibly overcome it is to identify what we call a falsification outcome. So that’s an outcome that you don’t expect to necessarily be related to the exposure of interest but is still sort of a negative health outcome. It’s related to utilization of the healthcare system and so forth. So we just chose respiratory infection, including influenza, pneumonia, and upper respiratory infections, and that’s ED or inpatient utilization for this falsification outcome.

So the idea is if long-term opioid therapy is associated with mortality and all these other things that we believe it should be associated with or could be associated with through some plausible clinical pathway, but it’s not associated with the respiratory infections that we feel better about these results, that perhaps they’re not exhibiting treatment indication bias.

Now it’s actually quite a challenge to find a falsification outcome for long-term opioid therapy. It’s become such a hot topic to study that many outcomes have been proposed to be somewhat related to opioids somehow, although respiratory infection was about the best we could do. That is our falsification outcome. But I would love to hear questions about that at the end or if there’s clinical input that disagrees with that, that you think opioids would affect respiratory infection rates, please do let me know.

All right, so how are we going to assess these associations? Well, we can do a basic unadjusted logistic regression and that’s just basically saying are these two things correlated. Do the Veterans who receive long-term opioid therapy have worse outcomes? Without worrying about any sort of adjustments or balancing, just say, take all the Veterans who received long-term opioid therapy and take the Veterans who didn’t within those first two quarters and compare their outcomes.

So we do that first. That’s always a great starting point. But then we start to try to balance our adjustments because remember there’s these potential confounders that could be biasing the relationships, and we can do these balancing in a couple of different ways. We did this with a logistic regression with direct adjustments, including generally all of the table one variables, including the adjustment variables. So I took an approach that most of the variables would be included in the model. I can provide the list later.

Then we also did the propensity score approach where we create a synthetic sample based on the probability of exposure. So there we’re modeling who got opioid therapy or not and trying to find people that are essentially quite similar in their probability of receiving it, even though they didn’t, one received it and one didn’t. It’s a bit more complicated than that. Probably worth of its own Cyberseminar at some point in the future, so I’ll leave it at that for now.

I did the inverse probability of treatment weights, and we trimmed the extreme weight values greater than 20, as you do have some very small probabilities that end up being really large weights can dominate your sample, so we did that as a sensitivity test. It was helpful to stabilize the results.

In general, the adjustment variables were all Veteran demographics, age category, gender, race, etc., urban and rural status, a wide variety of comorbidities at baseline, including a wide variety of pain conditions at baseline, neuropathic pain, back and neck pain, and so forth. Then we also analyzed prior and current quarter pain scores, both the mean and the max, and discretized that into groups, the idea being that a Veteran experiencing a large amount of pain or reporting high pain scores may or may not receive opioid therapy, but that may still be a high-risk Veteran. Right? So we want to be sure to adjust for that [inaudible 35:27].

All right, so that’s the setup. Let’s look at the results. In general, we first like to just kind of do a sanity check on our results. The number of Veterans in active primary care was increasing every year. So I identified every Veteran with a primary care visit and linked them and so forth. There was about four and a half million per quarter in 2008 up to over five and a half million in 2016.

So the number of Veterans in active primary care is increasing. However, in my cohort that I’ve built, this incident chronic pain or newly reporting chronic pain cohort, our numbers are kind of going down a little bit over time. Not dramatically, but certainly decreasing a bit. And what I think this is, is that I’m not allowing Veterans back in. So like once you’ve reported chronic pain, you can't report it again in 2014. Right? So there’s kind of a, you’re removed from the sample. I suspect that’s what we’re seeing here. So I think the population is probably getting slightly healthier over time due to the study design because people can't be coming in twice essentially. And we see that a little bit with the shape of that curve.

Our patient flow chart summarized. We ended up with about 2.6 million Veterans in active primary care, newly reporting chronic pain. So if we look at the differences of these Veterans, and I’ve got a really, of course, a large table one that will go to manuscript, but I’ve selected just a few relevant comorbidities that were, showed a large imbalance as denoted by the standardized mean differences. So in the first column here, we have no long-term opioid therapy initiation within the first two quarters, and in the second column we have long-term opioid therapy initiation within two quarters. I did do a sensitivity test to say within four quarters. The results were largely similar qualitatively for that, so I’m just going to present the within two quarters results.

What we notice is that, in general, the Veterans receiving opioid therapy, they’re more male, they are more whites. They have a higher prevalence of back and neck pain by quite a bit. They have quite a lower prevalence of gout. Other pain which includes things like central pain syndrome, chronic pain syndrome, etc., there is a pretty high amount as well, relatively speaking. So quite a bit of imbalance there.

Cancer of course, and we’ll bring this up again later when we look and think about do we really need to exclude the cancer patients, and perhaps we do for the mortality models, although I didn’t for what I’m presenting today.

Depression. This is a bit shocking that Veterans are more likely to be depressed that are exposed to long-term opioid therapy. This isn’t developing new depression. This is depression diagnosed in the prior year or the current quarter. Right? So this should be known at the time. Then of course the pain score; both the max and the mean pain scores are associated with long-term opioid therapy.

So let’s first look at our exposure over time. And this is the graph of this full cohort, 2.6 million Veterans. Among Veterans newly reporting chronic pain, generally we observe long-term opioid therapy is decreasing from 2008 to 2016, just as we would expect, and it’s similar to some of the results I presented earlier. There’s probably a little bit of two things going on here. I think there’s the decrease in, the policy of decreasing opioid prescribing in this newly reporting chronic pain Veteran population. Right? So these are people that are not already on long-term opioid therapy. They’re newly reporting chronic pain. They come to the VA, and do we initiate them on long-term opioid therapy?

It’s actually a bit above 15% in 2008 if we look at two quarters, and if we look at four quarters it was almost 20%. That decreases down to 5 and I think about 6% by the end of 2015. So we have substantial variation. So we keep thinking surely I can compare some Veterans from this first time period to some Veterans in this later time period that are very similar. It’s just we’ve changed how we care for them. And that maybe gives us an opportunity to identify causal effects between these relationships.

All right, so I’m looking at a wide variety of outcomes here. I detailed them earlier. Interestingly, if we were to just kind of globally look at the population and say what’s happening over time outcome-wise in this population, we do see a general decrease across the majority of these outcomes. These line types can be a bit hard to read. They are lined up, so death is the first one. Substance, alcohol, and other; falls, fractures; and so forth. So they’re lined up like that and if you can't quite make out the dots they’re in order according to their intercept on this side.

But we see that the mortality rate, generally decreasing a bit. Unfortunately, our respiratory infection really dives at the end. I think that’s an ICD-10, ICD-9 coding issue that we’ll have to sort out, although I spent some time trying to sort it out and unable to sort it out yet. But the rest of them all seem pretty stable or slightly decreasing. And again, this could be just due to the population getting a little bit healthier as we sort of weed out Veterans reporting chronic pain.

So let’s go on to the big results from the study. So this is now the pair-wise association across all of these outcomes. These are odds ratios from logistic regressions. Recall there’s three models. There’s an unadjusted model; the direct regression adjustment model, that was that logistic regression; and then the propensity score model. And in general, what we find is that in an unadjusted sense, there is a pretty substantially large association between long-term opioid therapy exposure and most of these outcomes.

So within mortality we see the odds ratio is 1.75 almost, which is really a large effect. And after adjustment for all of the things we’ve adjusted for, which is quite a long list of variables, it actually goes up. So we see the regression direct adjustment goes up quite a bit, and then if we take the propensity score up a bit more, although perhaps qualitatively similar results. So that association between mortality and long-term opioid therapy was quite resistant to adjustment. You can review the rest of these as well.

We see a similar sort of idea, although I started to see some instability in these propensity score estimates that makes me question them a bit. We do find the strongest association is with substance use disorder, opioid substance use disorder. However, that is the most rare outcome as well. Right? So if you recall from the prior slide, that’s a very rare outcome. But initiation of long-term opioid therapy does appear to lead to substantially increased odds of using the emergency department or having an inpatient stay where the diagnosis identified is substance use disorder for opioids.

Interestingly, respiratory infection, this is our falsification outcome. Now remember, this is the one we’re kind of hoping doesn’t have too much of a relationship with opioid therapy. Because if it does, we might be at a bit of a loss to explain it. We see that in an unadjusted sense there’s a moderate to strong, really it’s a moderate association, 1.3, something like that. I’ve got a table on the next page with all the exacts. But after we do regression adjustments, it goes down to almost nothing, 1.07. So that’s quite comforting, the idea that our falsification outcome is holding up, that respiratory infection after adjusting for covariates is not really related to long-term opioid therapy initiation, which implies that the other relationships we find might actually be real and not due to treatment indication bias.

However, the propensity score method identified a pretty large effect for respiratory infection. I’ve pushed that around quite a bit and I don’t fully understand it. I think I have to spend a bit more time with the propensity score results and perhaps do some other forms of propensity score estimation to better understand that. If you want to look at the summary of the outcome and all results, all the direct numbers are there.

So moving on to discussion then, really in summary we’ve identified a cohort of 2.6 million Veterans in regular primary care and newly reporting chronic pain from 2008 to 2016. There is a huge amount of variation in long-term opioid therapy initiation over this timeframe. It’s dropped by a third from 2008 to 2016.

However, the negative health outcomes that we think would be associated with long-term opioid therapy were not generally, they did not drop by a third. Right? The way that long-term opioid therapy did. But they were decreasing a bit and generally stable if not decreasing; certainly none were increasing.

So then the question becomes were they related to each other? We found that generally exposure to long-term opioid therapy was positively associated with all of the negative outcomes under study. And after adjusting for regression or falsification outcome, it was not very strongly associated at all. However, the propensity scoring office disagreed a bit with that.

So it’s a problem that possible residual or unmeasured confounding is indicated by that respiratory infection outcome. Right? Like we wanted to see the respiratory infection outcome to have no association, which would give us confidence that we don’t have residual unmeasured confounding. But that wasn’t quite true. However, that association was quite a bit smaller in magnitude than the other outcomes, leading me to think that sort of the gap between the two could be a real effect here.

So implications for VA policy. This was a huge undertaking, really, to get all of this work done. But I really view it as the first step of a bunch of work. We found that long-term opioid therapy was associated with a range of negative health outcomes. However, we’re not going to increase long-term opioid therapy exposure in the VA, right? So what’s actually actionable from this?

Well, I do think from a public health perspective we do want to quantify what is the actual reductions in opioid therapy exposure and how has that improved health outcomes? However, what is actionable is that we can use this framework to identify contextual factors that led to even better health outcomes. You can imagine that there are facilities where opioid therapy decreased and they had a large reduction in negative health outcomes, and there’s facilities where opioid therapy decreased but they didn’t get any reduction in negative health outcomes. Right? There’s probably a large amount of heterogeneity in these treatment effects. If that’s true, it would be wonderful to be able to identify those contextual factors that are modifiable so that we could start to inform polity in the future to say, yes, not only do we need to decrease long-term opioid therapy exposure consistent with VA policy, but these contextual factors seem really important to getting the positive health outcomes we want from those reductions in long-term opioid therapy. I view that in some next steps.

Talk about some strengths and limitations. I think this is really the first study of its kind in this scope. So I think that’s just a huge strength. And we viewed the observational EHR data. The VA actually has quite nice EHR data for Veterans that use the VA.

However, we have this presumption of no chronic pain if there’s no utilization. Right? Actually most of our variables are utilization driven. So if we don’t see a Veteran, we don’t see a pain score. We don’t see a diagnosis, etc. We do still ascertain mortality, and we do still ascertain opioid therapy exposure to the extent that, picking up their meds or we’re mailing them.

We did limit this quite intentionally to Veterans in active primary care so that we would have the ability to hopefully see a fair amount of utilization if they have it. The ED/inpatient utilization outside the VA is not great capture. Right? So I did include fee basis in these results. If the VA paid for it, then we got the records back; we do have that. But utilization the VA did not pay for we do not have access to.

So next steps. I think there’s a number of methodologic improvements to help disentangle these results a bit more. We might consider excluding cancer patients from the mortality models. I think some statisticians would push back on mixed effects models for the clustering by site. I actually think the results would be pretty robust to that. Generally that fixes standard errors rather than biased results. And when you have three million people almost, the standard errors become a bit less of a concern compared to the effect sizes, honestly.

I’m really excited about the possibility of leveraging site variation as an instrument. However, it’s been quite challenging to date. I’ve done a bit of work there, and I’ve not found it to be a valid instrument. But I think that’s still worthy of further study. And a finding facility is corners of the VA where we have sort of extreme behavior on one end or the other and comparing the outcomes of those Veterans who receive care at those corners of the VA I think is a powerful way to understand how our actions are actually affecting health outcomes.

I think another great next step, as I mentioned before, will be to identify the contextual factors that contribute to the treatment effect heterogeneity that almost certainly exists. So are there sub-populations of Veterans who really benefitted from decreased long-term opioid therapy exposure? And are there sub-populations who didn’t? I think that’s a very powerful result that should be further explored exactly in this cohort. And does exposure to other treatment modalities affect these relationships between long-term opioid therapy and health outcomes? I mean almost certainly. Right? Quality pain care is not just about reducing opioids. It’s about a number of other things, increasing other care patterns, so I think the context really matters. But we’ve certainly distilled it down to just decreases in opioids in this study.

Finally, we should expand this analysis to study the other populations of interest. Right? So there’s specifically Veterans discontinuing long-term opioid therapy. I think that’s another large population in the VA during this timeframe that we didn’t look at that will likely have just a different effect from opioid prescribing policy. And we’ll be looking at them next.

All right, I’ve got some references there throughout the talk. We’ve got time for questions. So thank you all so much for listening and feel free to send questions. Heidi or whoever is going to lead that, feel free to take it away.

Dr. Robin Masheb: [Unintelligible—cut off 49:38]. I’m not sure if everybody heard me. This is Robin Masheb again. Thank you, Dr. Carey, for a great presentation. We do have a lot of detailed questions about your study. But before I dive into those, I thought I would just kind of take a step back and talk about some big picture questions here and send these to Friedhelm Sandbrink because kind of the background for the study that you’re talking about is an area that is relatively new and controversial with regard to reducing opioid prescribing and even trying to withdraw patients who have been on long-term opioids. So to just give our audience some more background about that, I was hoping that Dr. Sandbrink could talk about the major factors that are driving both of those trends to reduce opioid prescribing overall and to even withdraw patients from opioids.

Dr. Friedhelm Sandbrink: Yeah, hi, this is Dr. Sandbrink. I hope everybody can hear me. This is obviously with, in response also in regard to specific questions and concerns that were raised in the chat. I think overall, and in the interests of time I have to just keep this brief, but I’d be happy to follow up individually later. But overall, what we’ve realized in the last decade or so, and Dr. Carey, your presentation was really phenomenal, in many ways highlighting also that this is in an approach that we’ve taken over many years already, way before we wrote out the opiate safety initiative formally in 2013, that we’ve realized that opiate prescribing is associated with significant harms. And that is, among others, the overdose stats with more than 70,000 patients in the United States being somewhat affected and related to opioids, both illicit and prescription opiate medications, with deaths per year. And it continues to rise. But also the development of opioid use disorder with more than two million people in the United States probably qualifying for a diagnosis of opioid use disorder.

But what we’ve realized also, and I think that it’s always important to mention is that we really have no evidence that long-term opioid therapy actually helps patients in the long run. And while it seems to have, in the beginning, and obviously it’s something, it’s usually always initiated in the best interests of the patient to try to, in the face of severe pain, try to get this under control. It really is, there’s no evidence that it helps in the long term. And you emphasized, you already mentioned the SPACE trial that shows that at least up to 12 months any initial benefit seems to be worn off.

So with that in mind, the VA and DoD, when they looked at the evidence, they actually recommended against the initiation of new patients on long-term opioid therapy. On the other hand, realize that being on opioids already is a particular challenge, and you can't just take opiate medication away because that’s associated with significant challenges in regard to patients who have developed physical dependence as well as also, and it’s, we realize that these patients, the Veterans who are on opiates, they actually have chronic pain. That’s why they’re on there. So you have to really institute either non-pharmacological and non-opioid therapies, and the goal is really to do this individualized.

I think, as was expressed in the chat, what we want to do is do this with a Veteran in mind for the best of the, to optimize the long-term therapy in regard to improving the pain situation. So our recommendation and our policy is this regard is if there’s a reduction, as reductions are being implemented that they are done very, very gradually with the patient in mind, with buy-in, active participation by the patient, realizing that involuntary tapers or that are not patient centered potentially put the patient at risk. So any dosage adjustment, especially in patients who are stable, need to be kept in mind. It this helping the Veteran? Are we improving function, both in the short term, and definitely is, are we successful in the long term? I just want to put that out there that the goal is really to improve the care of the Veteran, not just short term, but in the long term. Make it safer and more effective.

Dr. Evan Carey: And Friedhelm, I might follow up with you on that. I appreciate this is a sensitive topic. And thank you for the question from the audience member. I want to reinforce and reiterate that the clinical trial reference as well as this entire study is only focused on the population of Veterans newly reporting chronic pain, not currently exposed to opioid therapy. And as our audience member has noted, that is a small slice of the overall population. Right? So if we look back here, all of this work is really just on Veterans newly reporting chronic pain with the VA, not currently on an opioid therapy.

However, there is this entire subset of Veterans currently stable on long-term opioid therapy that are also affected by all of the policy changes and whatnot. And I think it is urgent, urgent for us to study and understand what the effects of discontinuation of long-term opioid therapy are on Veterans currently stable on long-term opioid therapy. I can promise you that I personally am working, really, as hard as I possibly can to urgently address that so that we can get those results back to leadership. I appreciate that question.

Dr. Robin Masheb: Thank you both so much. That was extremely helpful. We do have some specific questions, Dr. Carey, about your study. And maybe since you’re on the screen, talking about how the sample was arrived at for your study. Can you talk a little bit more about some specifics? For example, did the patient need to have, for the pain criteria, both the elevated pain scores and presence of chronic pain conditions? Was it one or the other? And can you talk a little bit more about the inclusion/exclusion of the cancer pain diagnoses or patients?

Dr. Evan Carey: Great question. Yeah. So at the end I’ve got a bit more details on that I’ll just leave up for people to read. But essentially the short answer is that they could have either patterns of elevated pain scores or patterns of diagnoses likely related to chronic pain, at least two over 90 days apart. So it’s a bit of a broad criteria. Right? So if I were to say I’m definitely identifying chronic pain, I think that would be an overly broad criteria.

However, I think in terms of filtering down to a population of interest to then assess these relationships with, we kind of went back and forth with Dr. Frank and some others on that. We were satisfied with that.

And what was the other question? Oh, cancer. Yeah, so I did not exclude Veterans with cancer. And I think that is really a tough point, especially when it comes to the mortality models in particular. So the association with mortality could be largely driven by Veterans with cancer. Actually when I review the adjusted results and we have the history of cancer, currently diagnosed with cancer in the prior year in this model and that regression model adjustment, it is a very powerful predictor of mortality actually, about twice as powerful as long-term opioid therapy. But it is in the model. So at least to the extent that cancer is measured and well-defined as a comorbidity, as we know, there’s probably some missing there. It is adjusted for. But I do concur that a sensitivity analysis excluding Veterans with, currently with cancer, perhaps with palliative care or some sort of, somewhere in between there would be intriguing.

Dr. Robin Masheb: Thank you. I’m realizing that we’re getting very short on time. Are there any other comments? We just have two minutes and I need to wrap up, but maybe one other comment either of you would like to share.

Dr. Evan Carey: Sure. Yeah. So quick questions, primary care visits identified based on clinic stop codes only in the VA. No Medicare visits were considered. To do a sensitivity test for those less than 65, actually it turns out a lot of the actions, so to speak, in this cohort in terms of long-term opioid therapy exposure is our Veterans 45 to 65. Other questions. A comment about opioid misuse, high levels of tuberculosis. Perhaps that explains respiratory infection anomaly. Yeah. Possibly. Thank you for that. It is such a challenge to find a falsification outcome for opioids due to the focus of searching for so many things that might be related to it in the literature. It becomes quite a challenge to identify something that everyone seems to agree is not related to opioid therapy.

Dr. Robin Masheb: Thank you so much, Dr. Carey. This was a really interesting talk, and I really appreciate our audience for writing in and also helping us to focus on the bigger picture here when it comes to talking about reductions in opioids.

Just one more reminder to hold another minute or two for the feedback form. If you’re interested in downloading the PowerPoint slides from today, you can go to the email you received this morning and look for the link to the presentation. All of our past sessions can be found by searching on VA Cyberseminar’s archive and use the filters to download previous sessions from Spotlight on Pain Management. You will also be receiving an email with your certificate of attendance for today’s session. Our next Cyberseminar will be the first Tuesday of October at 11 AM and you will receive a reminder email about the 15th of the month. I want to thank everyone for attending this HSR&D Cyberseminar, and we hope that you’ll join us again.

Heidi Schlueter: Thank you, everyone for joining us. As Robin said, please hold on for the feedback form. When I close the meeting out, you will be prompted with that. Thank you, everyone, for joining us for today’s HSR&D Cyberseminar, and we look forward to seeing you at a future session. Thank you.

Dr. Robin Masheb: Thank you, everybody.

[ END OF AUDIO ]