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Session: Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy:

A Systematic Review

Presenter: Joseph Frank, MD, MPH

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Dr. Joseph Frank: At the start I have no relevant financial relationships to disclose. I’d like to start by thanking a terrific study team that I have worked with on this project, folks from across VA and outside VA. It’s been a pleasure to work with this group and they’ve been a huge support throughout.

And so for an outline of today’s talk I’m going to start with a background which will be brief. I think likely everybody tuning in knows this issue and its context pretty well. Move into the methods of our systematic review, present our results, and then spend some time discussing implications. Hopefully those implications will aim at each of the different groups that we just now surveyed, and I’ll look forward to questions as we wrap up.

So to our background, we now know there’s inadequate evidence of long-term benefit of opioid medications for chronic pain, and in recent years there’s growing evidence of dose dependent harms. The figure to the right here is one that I think many of us know well, which shows the risk of opioid-related adverse events increasing with increasing dose.

To help providers balance the risks and benefits of opioids, the VA and Department of Defense released updated clinical practice guidelines earlier this year and spent considerable time in these guidelines on this topic of tapering long-term opioid therapy. I’m going to highlight a couple of the recommendations made in these guidelines that are relevant to today’s talk.

The first is that the guideline recommends against doses greater than 90 milligrams of morphine equivalent daily dose for chronic pain. So essentially aiming to prevent high dose therapy and prevent opioid tapering before it’s necessary. The guideline recommends for evaluation for tapering for all patients taking greater than 90 milligrams and for opioid tapering when in the course of this evaluation risks of opioids exceed their benefits.

The guideline adds a nice addition to this recommendation which is relevant to today’s talk that when recommending for evaluation of both the risks and benefits of continuing long-term opioid therapy. I’ll use this abbreviation LTOT throughout the talk a few times. Evaluation of those risks and benefits, along with the risks of benefits of tapering long-term opiate therapy, and the guidelines specifically mentions incident or newly identified opioid use disorder exacerbation of mental health conditions as risks of opioid tapering.

So what do we know about the risks and benefits of opioid tapering? There were, have been two recent published systematic reviews. These reviews included randomized trials and controlled observational studies and identified three small randomized trials and two controlled studies of opioid tapering interventions. Across these five studies there were 246 participants total and in both cases no conclusions were drawn from these reviews.

In addition to the lack of evidence on opioid tapering we know that this process is really quite challenging for providers and for patients. From our prior work conducting focus groups with providers, one primary care provider told us you see the person on the schedule and you know it’s going to be one of those just draining conversations. Another primary care physician said it’s my license that’s on the line for this. So I ultimately do get to choose. Obviously I do want to do shared decision making absolutely, but if a patient is not, you know, it’s on me ultimately.

We heard similar challenges when we interviewed patients, one of whom told us I also had lots of fears about let’s say there was an apocalypse in our society, what would happen to me? Where would I get my medication from? What was going to happen? And so in these interviews with patients we asked them to reflect on their prior experiences with dose reduction and this patient’s mind immediately went to thinking apocalyptically, giving a sense of how frightening and anxiety provoking this can be. Another patient said I have a tremendous fear in a doctor saying I want to taper you off the methadone and get totally off the methadone with no alternative whatsoever.

So to address these gaps and hopefully to inform tapering conversations between patients and providers, we sought to conduct a more comprehensive review of the literature and to synthesize all available studies of opioid tapering. So we identified two key questions at the outset. The first key question, what is the effectiveness of strategies to reduce or discontinue long-term opioid therapy? And our second key question, what is the effect of dose reduction or discontinuation of long-term opioid therapy on patient outcomes?

We pre-specified six patient outcomes, three which can be bundled as potential benefits: Pain severity, pain related function, and quality of life. And three categorized here as potential risks: Opioid withdrawal symptoms, substance use, and adverse events.

And to depict this one other way, we’re thinking about long-term opioid therapy for chronic pain and interventions to affect opioid dose reduction or discontinuation. And this is our outcome in key question one. In key question two then, dose reduction or discontinuation is the intervention itself and we’re interested in patient outcomes. And so I’ll move back and forth a little bit during the hour between key questions one and two.

And so to our literature search, we collaborated with a research librarian here at the University of Colorado to search multiple databases from inception through April 21, 2017. We reviewed reference lists of all included studies and of relevant reviews on the topic. We also surveyed expert context for additional recommendations.

For our inclusion criteria, we identified studies examining adults receiving long-term opioid therapy for chronic pain, and we defined chronic pain as greater than 3 months. Exclusion criteria, we excluded studies that examined acute perioperative or cancer pain only. We excluded studies in palliative care or hospice care settings. We excluded studies that looked only at elicit opioid use. We identified a few study designs which we were, which we opted to exclude, case reports, cross-sectional studies, and pre/post studies. When the intervention was not described in any way, we excluded those studies and we limited our search to English language studies.

So through this search strategy we identified 3,223 abstracts. Myself and one colleague reviewed each of these abstracts and eventually arrived at 67 studies that met our inclusion criteria. To look at these by key question, all 67 addressed our key question one about the effectiveness of strategies to reduce or discontinue long-term opioids, and 40 of the 67 provided data on the effect of dose reduction or discontinuation on patient outcomes.

We used the USPSTF criteria for individual study quality with two authors discussing and coming to consensus on all ratings. And we used the GRADE method for strength of evidence across our key questions, and all authors were involved in coming to consensus on these ratings. And I’ll spend just two more slides to give a little bit more information about these two methods.

So the USPSTF criteria allows us to rate individual study quality and gives us several different domains on which to think about this. We’re asked to think whether comparable groups were assembled initially. We’re asked to assess loss to follow-up during a study, to think about whether reliable and valid measurement tools were used, whether or not the intervention was adequately described. Important outcomes were considered, and in the analysis for observational studies, we’re asked to think about the author’s attention to confounders and in randomized controlled trials whether or not the intention to treat analysis was used.

To the GRADE method shown here is a schematic that describes starting with study design on the far left, rating the initial quality of a body of evidence, and then lowering or rating up that initial rating to arrive at one of four quality ratings on the far right; high, moderate, low, or very low.

So to the results of our systematic review, I mentioned that we included 67 studies. Across these 67 studies, 11 of these were randomized controlled trials, eight were controlled observational studies, and 48 were uncontrolled observational studies. And so this is one of the places where we hoped to extend the two prior systematic reviews that I mentioned by including these studies. And you see here that the majority of studies we included were uncontrolled observational design. As for our individual study quality ratings, three of the 67 studies were rated of good quality, 13 fair, and 51 studies by the USPSTF criteria were rated as of poor quality.

During this process we developed within our multidisciplinary team eight mutually exclusive clinical categories in which to group these interventions. And so you see these eight listed here. The numbers to the right are the number of studies in each category. So 31 of the 67 studies we classified as an interdisciplinary pain program. Ten we categorized as buprenorphine-assisted opioid tapering and on down the list. I will describe some of these in a little bit greater detail as we go forward during the hour.

Other results from the studies included. All told, these studies presented data on 12,546 patients. As we’ll talk about briefly, some of these studies were conducted at the same centers with overlapping dates and so these likely do not represent unique patients. The range across studies was five patients on the one hand to more than 1,400 patients on the other. Study follow-up ranged from five days to seven years. Forty-nine of the studies that we included were conducted in the United States, 11 in Europe, and five in Australia.

So next what I’m going to do is talk through the three good quality studies. I’m going to dive in more detail into these three good quality studies and then summarize I think some common threads across the three. The first of the three good quality studies that I’d like to describe is the study by Mark Sullivan and colleagues titled “Prescription Opioid Taper Support for Outpatients with Chronic Pain: A Randomized Controlled Trial.” This was published in the Journal of Pain earlier this year. So the intervention in this trial was an intervention which began with psychiatric consultation and medication review, followed with 18 weekly meetings with a physician assistant who had been specifically trained to deliver motivational interviewing and a cognitive behavioral therapy informed self-management curriculum for pain self-management.

The intervention used a protocolized taper which planned to start at a dose reduction of 10% per week initially. The primary outcome in this study importantly was opioid dose, and so dose reduction was the primary outcome. Secondary outcomes included opioid dose at 34 weeks, so further out, and then several pain and opioid-related outcomes as you see listed here.

Moderator: Joe, I’m sorry. I’m going to interrupt just a second, we got a…

Dr. Joseph Frank: Please.

Moderator: …request if you could slow down just a little bit?

Dr. Joseph Frank: Oh, sure.

Moderator: Thank you.

Dr. Joseph Frank: I will do so.

Moderator: Thanks.

Dr. Joseph Frank: And I’ll look forward to asking any questions if I move through any of the content too quickly at the end of the hour. Absolutely.

So shown here is the study flow. From 144 referrals, 35 patients were randomized in this trial. I think the authors in this manuscript, which is noted in the bottom left, do a nice job of discussing some of the challenges that they saw and then attempted to address with patients’ interest and willingness to be randomized to tapering support in a trial focused specifically on opioid dose reduction. And we’ll talk a little bit more about that later.

So 35 patients, 18 randomized to taper support and 17 randomized to usual care. You see in the box on the left side one participant attended no sessions, four participants attended less than 80%, and 13 attended more than 80% of all the sessions. Sixteen patients followed up in the intervention arm at 22 and 34 weeks, and 16 also followed up in the usually care arm at 34 weeks. And importantly the authors did use an intention to treat analysis in the results that we’ll see here momentarily.

So to describe in the, briefly the sample that was included in this study, this was a sample that was predominantly female, 67% in the intervention arm and 77% in usual care. Predominantly white. Pain duration was more than 10 years in three-quarters to 80% of the participants, so participants who had lived with pain for quite some time. A few more characteristics at baseline related to opioid medication use. Again about half had been on an opioid medication for more than 10 years. Opioid doses were above 50 milligrams in the majority of participants. They also assessed baseline characteristics or sort of self-reported characteristics related to opioids, and so they asked participants if they had tried to reduce previously and about 80% said they had tried to reduce their dose prior to enrolling in this trial. They further asked participants to identify one of two goals for their involvement in the intervention to reduce their dose or to discontinue. And about two-thirds of the participants noted a goal of discontinuing their opioid medications.

So shown here is the primary outcome from this study. Again, this is opioid dose at 22 weeks. The blue line is the taper support intervention, and the red line is usual care. And what’s seen here is that the opioid dose moved downward in both arms, both at 22 weeks and at 34 weeks. At 22 weeks, which is the box there in the middle of the screen, the adjusted mean difference between dose reduction in the two groups favored the intervention arm but was not statistically significant, and the same was true at 34 weeks. And so in short, the intervention did not increase dose reduction significantly, but we saw a dose reduction in both arms.

To look at dose reduction in this trial a slightly different way, shown here are categories of dose reduction across participants. On the far left is represented that the number of participants who did not decrease their dose from baseline through 22 weeks, and so four of 18 participants in the taper support intervention did not reduce their dose and eight of 17, about half of the participants in the usual care did not reduce their dose. You see there, 1% to 49% which was similar between the two groups and a greater proportion in the tapering support arm who achieved that 50% to 99% reduction cut-off. To the far right then, you see that one participant in each arm discontinued opioids completely by 22 weeks.

So to look at the secondary outcomes, I’ve just selected two outcomes that were found to be significant in this, in the, in this trial. Shown on the left is pain interference which was significantly improved in the intervention arm at 22 weeks. And pain self-efficacy also significantly improved in the intervention arm at 22 weeks compared to usual care.

So from there I’m going to shift gears and move onto the second good quality study that we included in our systematic review. This is a randomized controlled trial of mindfulness meditation and CBT-based intervention versus usual care published last year by Zgierska and colleagues. The intervention in this randomized trial consisted of eight weekly two-hour group sessions as well as 30 minutes per day and six days per week of at-home practice. The mindfulness techniques as they’re described included breath, body scan, and walking meditation among others.

So primary outcomes in this trial were pain severity and function, importantly a difference with the prior trial is that opioid dose was not a primary outcome, so opioid dose was a secondary outcome and it does not appear that dose reduction was, was mandatory or specifically encouraged as part of this intervention. The authors did, I think, a very nice job of measuring several other secondary outcomes including pain sensitivity testing and biomarkers.

So a similar study flow diagram here. From 87 participants assessed for eligibility, 35 were randomized to either the intervention, 21 participants on the left, or to usual care. And you see in that big box on the left that 19 of the intervention participants participated in at least one session. Twenty out of 21 were followed at eight and 26 weeks. Thirteen of 14 in the usual care arm followed up to 26 weeks, and again, an intention to treat analysis was used in this trial.

Sample characteristics, I’ll try and point out some of the similarities with the prior trial here. Again, a majority of participants were female. The majority were white. Pain severity rated as moderate in both groups. And the mean opioid dose in the intervention arm was 167 milligrams daily at baseline and 120 milligrams daily at baseline in the control group.

So outcomes in this trial. I mentioned primary outcomes related to pain. Pain severity was significantly decreased in the intervention arm versus control. In secondary outcomes you see in the second bullet point, they found no significant change in mean opioid dose, both between groups or within groups. You see trends in that direction in the figure on the right. The blue line is the intervention and the opioid dose trended downward, whereas the usual care, the control group, remained mostly flat but that was not a statistically significant difference. The authors did also report on the proportion of participants on greater than 200 milligrams, so the proportion on very high-dose opioid therapy, and reported that this proportion decreased in the intervention arm from 29% to 20% at 26 weeks, whereas it increased slightly from 21% to 23% at 26 weeks in the control.

Moving on, the third good quality trial, and then I will wrap up by, I think, highlighting some common themes across the three was a randomized controlled trial of four-month therapeutic interactive voice response, or TIVR, plus standard care versus standard care only. This is a study by Naylor and colleagues published in 2010. The intervention was an automated telephone-based tool developed for the maintenance and enhancement of CBT skills, and I’ll describe a little bit more about that momentarily. The authors describe an optional goal of opioid dose reduction and specifically note that among participants who identified this as a goal, this goal was reinforced by individualized content in the intervention program.

So similar to our second study, the primary outcomes were pain-related outcomes and it was a secondary outcome that related to medication use, specifically opioid use.

In our third study flow diagram here, we see that 67 participants completed an 11-week group CBT course, and so these trial participants here were recruited from among a group who had already participated in this 11-week program. Fifty-five of the 67 elected to continue on into this randomized trial and 29 were randomized to the intervention and 26 were randomized to standard care. Similar to what we’ve seen but with different time points, they completed follow-up at four months and eight months in both arms and intention to treat analyses were used.

Sample characteristics. Again, we’ll start to see some common themes here. In this study, a majority of patients were female and a majority were white, pain duration of 13.6 years in the intervention arm there in the middle row and 8.6 in the control, so individuals who had lived with pain for years. And then to look at baseline medication use, 54% in the intervention arm and 72% in the control arm on opioid medications at baseline, and so some who came to this trial not using opioids regularly. And then three other pain-related medication classes that the authors describe as well.

So to our outcomes, I think similar to the second study which we discussed pain outcomes, I suppose similar to both studies pain outcomes improved in the intervention arm compared to the control. Mean opioid dose as a secondary outcome decreased in the TIVR arm, the intervention arm, and increased in the control. And so you can see that in the figure on the right. The black bars represent the intervention arm. At baseline prior to the 11-week course, post CBT at the baseline point for this trial, and then post TIVR intervention at four months, and then still later at eight months as we work left to right. And you see that the black bars trend downward and there are tests of significance shown, whereas the white bars trend upward to the eight-month follow-up point, and there’s the test of significance shown there as well. So these are significant findings. The authors also report on discontinuation in addition to reduction in the intervention arm. Three subjects had discontinued opioids by the eight-month follow-up, whereas in the control three subjects had newly initiated opioids at eight months. They’re moving in different directions.

So to summarize these three good quality trials that we included in our systematic review, I’ll point out a few similarities. One of the three good quality randomized controlled trials demonstrated significant opioid dose reduction versus control. So this was the study by Naylor and colleagues. There was significant benefit on pain outcomes in all three trials. I think other similarities was the dose reduction was supported but not mandatory in each trial. Now in the trial by Sullivan and colleagues dose reduction was the stated goal of the intervention. Per their reporting, dose increase was not allowed, but as we saw, several of the participants remained on their same dose throughout the trial.

Common themes included that the interventions in all three were informed by cognitive behavioral therapy and really took sort of a multi-modal and sort of multi-skilled self-management approach. Importantly, none of these three good quality studies reported patient outcomes of dose reduction. In other words, as currently reported these three trials do not allow us to specifically identify only those patients who discontinued or reduced and how their outcomes were impacted by that dose reduction or discontinuation.

So in the next phase of our results I want to focus on our interdisciplinary pain programs that were included in the review. So as a reminder, these were 31 of the 67 studies included. These 31 studies took place at 19 intensive interdisciplinary programs, so several of these programs publishing two or more studies of the work that they’re doing. The majority were in outpatient setting, 21 studies. Eight studies were in inpatient settings and two studies described programs that bridged inpatient and outpatient settings.

A typical duration was three to four weeks. There was heterogeneity across these programs as to how long these programs lasted, but that was typical. Nearly all emphasized the biopsychosocial model of chronic pain and emphasized delivery of multi-modal care. Opioid dose reduction was mandatory in 27 of the 31 studies. To our USPSTF quality ratings, zero of these studies were rated as good using these criteria. Eleven were rated as fair, and 20 were rated as poor quality.

I’m going to highlight two recent studies of interdisciplinary pain programs and hopefully use these as examples to think about some of what we learned across these 31 studies. The first is a study by Murphy and colleagues published last year. This was a study that looked at care provided at the Chronic Pain Rehabilitation Program at the Tampa VA from 2006 to 2011. In this analysis, they identified 324 participants who completed data collection at program admission, discharge, and three-month follow-up and had the specific aim in this analysis of comparing treatment outcomes among male and female participants.

In a paper by Huffman and colleagues published earlier this year, they examined the interdisciplinary comprehensive pain rehabilitation program at Cleveland Clinic from 2007 to 2012. They included 1,457 participants admitted to the program and sought to compare treatment outcomes across opioid use groups classified into none, low-dose, or high-dose therapy.

Now I’ll briefly describe the results from each of these studies. In the study by Murphy and colleagues, at baseline 35% of participants were on opioids, 100% discontinued by discharge. And this was a feature of the study design as they included those individuals who had completed and been discharged from the program. To look at another study published by this same group from the same program, they reported 85% completion in a prior study, and so nearly all participants who begin the program are completing the program. In this study, they found that 17% of individuals who had been discharged and followed up at three months reported opioid use at three months. And so some individuals had reinitiated opioids after discharge. Among all participants, they noted benefits at three months and multiple pain outcomes. And importantly in this study, these outcomes were not stratified by opioid use at baseline.

Now to compare to this study we’ll look at the results from the Huffman study from 2017. In this study, 65% of patients were on opioids at admission, 87% of individuals on opioids at admission were discontinued by discharge, and across all participants they described a program completion rate of 82%. And I would say across these studies these are pretty typical of the discontinuation rates. Certainly some were higher and some were lower, but these are fairly typical of what we saw across these studies. They described opioid re-initiation at six or 12-month follow-up and found that among individuals in the high-dose group, 33% had reinitiated; among the low-dose group, 29%; among the no opioid group who had not been on opioids at baseline, 10% had newly initiated long-term opioids at six or 12 months.

They did describe benefit in multiple pain outcomes at discharge and sustained at six and 12 months compared to admission. And they did stratify based on opioid use at baseline and found that these effects did not differ based on opioid group. In other words, the participants who had been on opioids at baseline benefited similarly to those who had not.

So to summarize across these 31 studies, and again highlighting the two that I have just now, we found that interdisciplinary pain programs can effectively support voluntary relatively rapid opioid dose reduction. Again, I mentioned a mandatory goal of dose reduction in the majority of these studies, and many of them typically lasting on the order of several weeks. Studies did report re-initiation of opioids occurring in a substantial minority of participants after program completion.

And finally I want to spend a few minutes focusing in on one of our six pre-specified patient outcomes in key question two. And so this key question aims to identify the effect of dose reduction on pain severity, and I’ll describe what we found a little bit for this specific outcome. Among our included studies, we identified 36 studies that examined the effect of opioid tapering on pain severity. Across these studies, 29 of the 36 studies reported improved pain, four of 36 reported no change, and three of 36 reported worsened pain. Now across these 36 studies, there were eight fair quality studies, the remaining were poor quality. And of note, eight of eight, so all the fair quality studies reported benefit of opioid tapering on pain severity.

To think about sample size, we also looked at this key question by pulling out those uncontrolled observational studies that had smaller samples, less than 50 participants, and found that 22 of 28 studies reported benefit when removing those smaller uncontrolled studies.

And finally, we’re able to look across intervention types. Of the 17 interdisciplinary pain program studies that examined the effect of tapering on pain severity, 14 reported benefit. And of the eight buprenorphine studies, all eight reported benefit with transition from full agonist opioids to buprenorphine.

So I want to spend the next few minutes thinking a little bit about implications of this work and then hopefully have plenty of time for questions from the audience. I’m going to work through these implications thinking about different audiences and start by thinking about implications for clinicians.

To our key question one, we identified multiple intervention types that are effective to reduce or discontinue long-term opioid therapy. Importantly using our grade system for assessing strength of evidence, we did assess this to be very low strength of evidence based on the limitations of the studies included. So from there we recommend considering referring patients to a multidisciplinary pain program if available to support opioid dose reduction. Again, 31 of 67 studies took place in such a multidisciplinary pain program setting. Where not available, which I think for many primary care physicians is a common barrier, it will be important to identify feasible strategies for building multidisciplinary tapering support in primary care settings.

There is inadequate evidence of comparative effectiveness of interventions. So it is at this point I think quite challenging and left up to expert opinion still to identify whether one type of intervention is going to be more effective for a given patient than another.

So still thinking about implications for clinicians to our key questions two, described pain, what I didn’t mention is that function and quality of life had very similar findings, and so we can say that pain function and quality of life may improve after voluntarily opioid dose reduction. Importantly across all of our pre-specified patient outcomes in key question two, we rated the strength of the evidence as very low. And I think also importantly in this sentence I’ve noted voluntary, and I think this is key consideration here is that the studies that we included were programs that required voluntarily participation or trials that required informed consent to participate, which may not reflect or may not generalize to some of the patients that clinicians are thinking about as they tune into this talk.

Finally there’s inadequate evidence to guide assessment of the risks of tapering. We looked at adverse events, which was described in 11 of the studies we included, and subsequent substance use, which was described in only four, but we also identified studies that stratified by baseline substance use. Five out of the included studies did so and so really provide inadequate evidence at this point to assess the risk, particularly in high-risk patients for whom concurrent substance use is a concern during the course of opioid therapy.

So I’ll note just a few unanswered questions I think from this work that I think are, are pertinent to providers, pertinent to prescribers who may be attempting to guide patients through opioid tapering, and the first is rate of tapering. To make a few notes from the studies that we’ve discussed, I mentioned that the trial by Sullivan and colleagues started out with a rate of 10% per week. On the other end of the spectrum perhaps, discontinuation was conducted over three to four weeks in the interdisciplinary pain programs that we evaluated, and so a much, a relatively more rapid dose reduction. To compare this to guidelines that we currently have to work from, I think that 10% per week figure aligns nicely with the CDC guidelines, but those CDC guidelines also acknowledge that slower rates are likely necessary if patients had been on medications long term. And then the VA and Department of Defense guidelines which I highlighted earlier give a similar range looking at 5% to 20% per 28 days.

And I think a second important but unanswered question for clinicians is how best to manage concurrent substances. What are the risks and potential benefits of concurrent marijuana use in the setting of long-term opioid therapy and concurrent benzodiazepines in long-term opioid therapy? What are the best strategies to engage patients in discussions of tapering and how best to reduce that medication combination? Neither of these were adequately addressed in the included studies, and so again, for clinicians this remains left up to the strength of evidence of expert opinion.

So moving on to think a little bit about implications for researchers, I’ll name a few key points here for those of you who come to this talk through a research lens. I think the first is that consensus is needed on measurement and reporting of opioid tapering. We saw a wide range of how this was reported in the studies, mean and median dose at base line and at follow-up, categories of dose proportions on high-dose, etc., and so this makes a comparison across studies challenging. I think consensus will be helpful for future studies and probably lands around authors presenting multiple domains, so tackling both overall reduction and proportion of patients who reduced and discontinued can each give a different view to what happened in the intervention.

So second, recruitment to trials of opioid tapering will require innovative strategies, both for recruitment at the time of enrollment when describing the trial and for retention across the trial. I think this recommendation builds on some of those issued by Sullivan and colleagues in their paper that I alluded to and some of the challenges they faced. Certainly randomizing patients to interventions with greater control left in the hands of the patient is likely to enhance enrollment. And I think importantly both for research and for clinicians, understanding the most effective strategies for engaging patients in this conversation, for assessing importance and readiness, and for supporting behavior change are all areas in need of additional work.

Post-hoc analyses or prior pain management studies may prove, provide additional insights on those reduction and/or outcomes. In the process of reviewing and then excluding several pain studies, it’s clear that those studies would have included patients on long-term opioid therapy and likely collected data on how opioid prescribing changed throughout the trial, but reporting in the initial manuscript or subsequent manuscripts doesn’t allow for the inclusion in this systematic review. But with limitations, post-hoc analyses may add to the evidence that we currently have.

Future studies should examine interventions that are feasible in primary care settings and adaptable across clinical settings. And so I think at the outset it was a minority on the call who are primary care physicians. That’s where I practiced medicine and it’s the setting that’s nearest and dearest to my heart. Five of the studies that we included out of 67 included primary care settings, which is where a majority of opioids are prescribed, and so it will be an important focus and a particularly challenging one where primary care docs and their teams are already very busy.

Two more implications for researchers; I think it’s important to think about the natural experiments that are happening in health systems and states currently. Seen here on the right is a figure from a paper published just this morning in JAMA Internal Medicine looking at VA data. The curves here show a general similarity across three prescribing patterns in VA showing decreased prescribing. The orange curve there shows that over 15 years or so about 100,000 fewer Veterans are receiving high-dose morphine. So this is already happening both within VA and elsewhere. Certainly in a system like VA, these policies are going to be implemented differently at different institutions, at different rates, at different facilities, and potentially quasi-experimental designs taking advantage of this variation can help us better understand current opioid tapering practice and can help us understand how this variation affects patient outcomes.

And then finally surveillance of efforts to reduce opioid prescribing is needed to inform the assessment of risks and unintended consequences. And so I think prescribers who have been through this conversation can probably think of the patients in whom they were worried that the potential harms of dose reduction were very real. And these are probably rare enough that they will be challenging to measure, and so health system level analyses or surveillance and other large datasets will be an opportunity to understand unintended consequences of opioid tapering.

And I’m just going to close with two additional implications for policy makers and funders. Importantly what we didn’t find were studies of outcomes following involuntary tapering among otherwise stable patients. I think in different states these experiments are playing out currently. I’m just going to mention briefly something that I think made news recently in Maine. I don’t claim to be an expert on how things are happening in Maine but thought that this was a useful example. Here in a couple of months there will be an opioid dose limit of 100 milligrams daily. And just recently in March, a new bill was put in place to clarify how providers cannot assert medical necessity for patients who they believe are best suited to continue on high-dose therapy.

And so what this bill sets out is that those providers would be asked to conduct a history and physical, a failure of non-opioid treatments, risk assessment and mitigation, I think all of which sound a lot like guideline concordant pain care. The thing goes on to note that providers must confirm that a taper trial resulted in significant loss of function. And so, you know, this bill would ask providers to taper opioid medications, identify that loss of function occurs, and then pull off. And so I think this is a real challenge for patients and providers to respond to such policies in the absence of evidence.

And then finally to funders, I think continued funding is needed to support high quality studies and to strengthen the evidence. We did look at funding sources across these studies, and the vast majority of them reported no funder or identified being unfunded. And so I think going forward, rigorous data collection, certainly resources to maximize follow-up will help strengthen the evidence. I’ll close with one note describing one source of funding that in the years ahead will add to what we know about opioid tapering. The Patient Centered Outcomes Research Institute funded two studies recently, and I believe is currently reviewing additional studies in this domain. The first is a comparative effectiveness trial led by Aleksandra Zgierska and colleagues, and we saw her trial a little bit earlier. And the second is the comparative effectiveness trial in the VA led by Erin Krebs, and so both of these studies will make valuable contributions to this evidence.

With that, a quick slide showing some of the resources that I have discussed. I alluded to the VA and DoD guidelines. I mention here a link to a VA Opioid Tapering Decision Tool, which I encourage people to take a look at, and then there’s some CDC guidelines as well with links to their resources.

With that, I will again say thanks to my team on this project and look forward to questions in the remaining 15 minutes.

Moderator: Wonderful. Thank you so much. We do have some pending questions here. For the audience, please feel free to send in those questions. We should have time to take a few more than we already have received. I’m just going to start at the top here and work my way down. How are the guidelines adjusted for patients who consume alcohol or other meds/substances that could interact dangerously with opioids?

Dr. Joseph Frank: So I think that’s an important question. I think I will attempt to answer it first from the view of our systematic review. I noted there toward the end that five of the studies that we included in this systematic view stratified their analyses, stratified their outcomes by baseline substance use and so really very few of these studies. And so I think at this point based on the studies we’ve identified for our systematic review, we can’t add a great deal for that question and I think it’s critical. To the question I think mentioned the guidelines. Certainly the CDC guidelines and now the VA and Department of Defense guidelines each agree on the goal of assessing risks and benefits, and so to the extent that concurrent substance use increase risks that outweigh any benefits, tapering then would be appropriate. Hopefully then this evidence can provide some guidance, I think, that tapering for some patients is actually going to improve pain function and quality of life. And perhaps including that in conversations with patients is going to be a valuable place to begin talking about the role of dose reduction.

Moderator: Great. Thank you. The next question here, has there been any research on involuntary tapering? If not, do you have any speculation about how effective involuntary tapering is likely to be at pain reduction and other desired outcomes?

Dr. Joseph Frank: That’s an excellent question. So involuntary tapering, I think I, I tackled that briefly there at the end, and so I think to answer the question very simply, no. And then I would gladly try and speculate. I think I would have maybe an answer in three parts to my speculation about how that would happen. I think that patient engagement is likely important mechanism by which patients are able to reduce their dose and able to reduce their dose with beneficial outcomes in other domains. I think when the tapering is involuntary or I suppose quasi-voluntary that it likely for providers makes that patient engagement more challenging. And so I think it sets the process up to be more difficult from the outset I would predict for many patients and providers. You know, we will speculate it as we discuss these findings in a manuscript as to what the mechanism might be for benefits and pain function and quality of life to the extent that medications are causing side effects that adversely impact quality of life, perhaps amplifying pain. Their reduction improves those outcomes. I think it’s reasonable to expect that for some patients tapering involuntarily they will still, you know, those mechanisms will still apply and they may experience benefits.

And then the third domain of my answer that I would say is I think that for patients tapered involuntarily, particularly involuntarily in the setting of high-risk behavior, those are probably the patients who are at highest risk of adverse events. We don’t yet know how, how common those are, what risks to be most concerned about, and how to individualize that assessment to patients. And so that’ll be important going forward. But I think that’s an important question and a timely one that, you know, hopefully we will learn more about in the years ahead.

Moderator: Great. Thank you. The next question here, do you have tips for engaging patients in tapering conversations?

Dr. Joseph Frank: I do. I think one of the strategies that I have incorporated into my conversations about opioid tapering that I find to be quite helpful is to identify that overall improvement and quality of life function and pain is possible. I will recommend to my patients that that is my goal; that my goal is not about a dose, that reducing the dose is a means to an end of feeling better. I think this systematic review, again, with the strength of evidence that we described as very low does suggest that that’s a reasonable statement to make to patients. And so I would encourage that, and I’ve certainly done that with my patients.

I think the second recommendation I would make, which we see in some of these studies relates to the rate of tapering. For patients in whom tapering is not emergent, rapid tapering is not indicated, I think slow tapering offers a much different approach than faster or less, less adaptable tapering. And so I will turn it over to my patients to let them know that we will take this one step at a time. We’ll agree on the overall goals but assess frequently, that we can pause the taper as we go. You know, I think we saw similar pauses happening in the first trial that we talked about by Sullivan and colleagues, and so I think that is an appropriate way to manage this process and I think can be a very reassuring statement to make up front in opioid tapering. And so I’d recommend including that in the conversation as well.

Moderator: Great. Thank you. Next question here, did any of these studies discuss opioid-induced hyperalgesia, particularly the studies that assessed pain sensitivity?

Dr. Joseph Frank: I think that’s an excellent question. There were a few of the, I believe we included two studies whose primary aim was to assess pain sensitivity, and you know, we sort of poured over the results that they reported to identify their application to our key questions. So we did include a couple of those studies. You know I think based on those two studies I don’t feel like I am yet an expert, and we may have those experts on the call for some of those pain sensitive, pain sensitivity testing techniques. I think better understanding of that, of that phenomenon will be important. I find that to be a very challenging topic to concisely and clearly communicate to patients. I think going forward, resources that can explain that both to providers and help them explain, explain the role of hypersensitivity and hyperalgesia to patients is going to be important. We do, I think, plan to discuss that as one of the potential mechanisms, and so I think it’s an important piece of this potentially for why some patients may benefit with dose reduction.

Moderator: Great. Thank you. The next question here, I think the answer is no, but is there an agreed upon level of dose reduction that is considered meaningful from a research perspective?

Dr. Joseph Frank: I think there isn’t currently. So I agree with no. I think that is an important, an important next step. I am involved in a couple of projects to just speak from my own experience in which we have used a cut-off or planned to use a cut-off of 50% to argue that that’s a clinically meaningful dose reduction. I have also experienced adapting at least one study in a benzodiazepine tapering intervention in which they used 25%. I think frankly either of those is, either of those are appropriate. I might recommend that researchers make plans to identify primary outcome but also make plans to present to reviewers and readers several other cut-offs because I think they can provide additional nuance to what’s happening within a population that’s being studied. So I also think the answer is no, but I think it’ll be an important next step in finding consensus.

Moderator: Great. Thank you. Two questions here that are somewhat similar, did any of these studies monitor illicit drug use, elicit opioid or other during the interventions to supplement the tapered prescription opioid regimens?

Dr. Joseph Frank: I think that’s a good question. And so we identified four studies that reported on measurement of substance use. In each of those they reported on measurement of illicit substance use or non-medical use of prescribed opioids. The rates varied widely across those four studies from sort of one study reporting less than 1% to a couple of studies reporting 63% and 64% of participants. Again, those were four small studies including 204 participants across the four studies, and all four we rated as poor quality. And so drawing inference from those is, I think, quite difficult. I think the guidelines would recommend that during opioid tapering close monitoring of risk including concurrent substance use, illicit substance use is a good idea. And so I think what would be helpful from future studies is to understand which patients are at higher risk, perhaps which risk monitoring tools are most effective, but in the meantime I think we probably all follow the guidelines and use the tools we have.

Moderator: Great. Thank you. The next question here, do prescribers view opioid tapering for the elderly who have been on them for many years as futile? And why not just keep them comfortable? And are there any studies for the very elderly regarding opioid tapering?

Dr. Joseph Frank: I think that’s a very good question. So there were, maybe to answer that, the second question first. None of the studies we included specifically identified, I believe, certainly it was not a common area of study. I want to say that none of the studies specifically identified an older adult population. I think to the first question why not keep patients comfortable, particularly patients who have been on an opioid medication for many years, I think that the current guidelines would support that among patients in whom the benefits outweigh the risks. And so I would agree with that statement. I think that approach for patients who are on high-dose therapy that runs afoul of state regulations or other policies that are taking a population level look, those recommendations will collide. And so I think that will be a real challenge for providers to navigate the patient whose dose is higher than a policy cutoff but in whom benefits appear to be outweighing risks. And so I imagine many on the call have seen those challenges already, and it seems as though that’s only going to increase near ahead.

And the third thing I would say is an older adult population is probably one in whom alternative medications may be relatively contraindicated compared to younger patients who have more options which makes tapering more challenging. We saw many of these interventions use multi-disciplinary approaches. Use other medications for pain. Use other medications for management of withdrawal. And in a population where medications side effects, contraindications, and interactions are going to be more problematic, those approaches are going to be limited.

Moderator: We just got a comment in from someone in the audience, just a comment about opioids and the elderly. Unfortunately long-term use of opioids may interfere with cognitive function. Hence providers are put in a position where they don’t know if the cognitive impairment is a dementia or a consequence of the opioids.

Dr. Joseph Frank: I think that’s an excellent point. I think one other thing, back to the question about tips a few questions ago, I think I try and frame opioid tapering as a trial. When, you know, when that’s, when I’m able to do so. And I think in a patient, in an elderly patient who’s having some cognitive impairment, you know, I think my approach would be to recommend a trial of opioid tapering to understand whether or not the medication is involved. Certainly it would make me very hesitant to begin talking about a diagnosis of cognitive impairment, a diagnosis of dementia in an older adult on opioids. And so I think a trial of tapering would be appropriate to understand whether or not those symptoms or side effects.

Moderator: Great. Thank you. Oh, we are just about at the top of the hour here. It looks like we actually just have four pending questions left. So if you have the time, I know some of our audience may need to leave. We are recording this session. We will have a transcript made of the session. So if, Dr. Frank, you’re able to stay on and hopefully get through these last four questions. If our audience does need to leave, we should have that information captured in those areas if you submitted a question and we haven’t been able to get to it yet. Also Dr. Frank’s email address is on the screen right now. If you do have, if you do have a question he should be able to help you out there if you have not been able to get that sent in to us yet.

The next question we have here, did any of the studies report on the scripting that was used by researchers in their efforts to induce willing participation?

Dr. Joseph Frank: They did not. They did not. I think that’s an excellent point. I mentioned strategies for recruitment, enrollment, and retention, and I think careful scripting of the conversations certainly at the front end of engagement with the potential participant seems like it could have important implications to that person’s interest in the trial and willingness to hear more. And so I think that’s an important question. I thought where the question was going was a question of scripting between clinicians and patients, and I think similarly, I think arriving at some agreed upon language that is most useful for patients, is most patient centered and accurate I think will be important both for recruitment and for clinical care.

Moderator: Thank you. The next question here, were reinitiated opioids self-reported by study participants or was the information obtained from their medical record. If unsure, would you suggest using patient reported, medical record abstracted, or both?

Dr. Joseph Frank: There was heterogeneity across data collection methods in the study. And so some studies used either and some used both. I think it would likely for researchers or program evaluators be more resource intensive to use both, but I think that probably provides valuable either confirmation or disagreement between the two. Increasingly, a third option in some states depending on the statute may be a prescription drug monitoring program. You know, I think I’m familiar with some challenges to using our resource locally for research, but that could be a third opportunity to understand if patients have resumed prescription of the controlled substance.

Moderator: Great. Thank you. The next question here, what is your opinion on how the intervention of tapering was presented to patients prior to application of inclusion or exclusion criteria in these studies? In other words, were the patients in the study well informed of risks versus benefits of long-term opioid tapering before volunteering to taper or not taper?

Dr. Joseph Frank: Well, I think the answer to that question differs based on the study. And I think I’ll include two examples that we discussed today, the first being the randomized trial by Sullivan and colleagues in which they were specifically recruited to an intervention for opioid tapering. I think importantly they describe difficulty enrolling participants and that may be a result of participants understanding well that that was a goal and not being interested. They also, I mentioned that they asked participants about a goal and so participants were specifically asked to name a goal for dose reduction either to reduce or discontinue. You know, I think some of those pieces of feedback are probably useful tools to confirm that patients understand what the objective of a trial like that one is.

The second point I would make would be to reflect on the interdisciplinary pain programs that we discussed. I think many of those programs dose reduction was mandatory, and so the patients who are being admitted to those programs will have, will have likely heard of that program requirement. Certainly most of those studies described rates of program completion, and so some of those patients did not complete the program. I mentioned high 80% or sort of in the 80’s is where many of those programs describe program completion. And so some proportion of those, you know, had discordant expectations or didn’t expect tapering to be a role. You know I think the challenge is that there’s likely heterogeneity across how those expectations are presented and an opportunity perhaps for programs to attempt to use similar language that’s likely to be most effective.

Moderator: Great. Thank you. The next question here, did any of these studies address the frequency of declaration by patients’ behavior of substance use disorder unearthed during taper?

Dr. Joseph Frank: That is a very good question. I think, you know, the way we attempted to classify that in our approach was, would probably best have been captured with subsequent substance use. And so I think of note that was collected in four of the studies we included. And I think an important way is different from a diagnosis of an opioid use disorder. And so I think the short answer to that question is no. That’s certainly an important outcome in the tapering process and one that among the studies that we included we don’t have much to say at this point. But I think an important question and one where we would certainly benefit from having a good understanding, you know, just of even the first estimate of what proportion of patients undergoing tapering identify an opioid use disorder during the process. I think at this point our included studies can’t answer that question.

Moderator: Great. Thank you. And then one last hopefully short question, how long can people stay on methadone treatment?

Dr. Joseph Frank: Depending on the indication. There isn’t anything that we learned in our, in our review here, I think to answer that question directly. I think depending on the indication whether for chronic pain or for a treatment of an opioid use disorder, the answer probably differs. I think the answer for patients prescribed methadone for chronic pain, per the guidelines at this point would be for as long as benefits outweigh risks. And I think that’s going to vary widely given, given, given different patients. I think it’s an important question and not one that our systematic review is well positioned to answer. I think importantly across all of our studies many of these programs and studies describe patients who had been in chronic pain for a decade and on opioid medications for many years. And so they were taking place among participants who had been on medications for many years. But we weren’t able to specifically drill down on methadone or any other specific medication, and so I don’t think our systematic review can shed light on that question.

Moderator: Fair answer. Thank you. That actually wraps up all of the questions that we have received. Before I close out, Dr. Frank, did you have any closing remarks you’d like to make before we wrap it up?

Dr. Joseph Frank: Oh, I think I, one last closing remark would be to thank you, Heidi, for your help with the session and for the opportunity to present our work. So thank you.

Moderator: Oh, we are happy that this forum is available for you. We love having you guys come in and present. There’s also great discussions, great conversations, and especially the audience here submitted some great questions that really created something extra for today’s session. So thank you very much for presenting today.

[ END OF AUDIO 1:04:54 ]