Cyberseminar Transcript

Date: August 27, 2019

Series: Spotlight on Evidence Synthesis Program

Session: WG2 - Benefits and Harms of Long-term Opioid Dose Reduction or Discontinuation in Patients with Chronic Pain

Presenter: Kate Mackey, PhD

**Rob:** Hello everyone. This is Rob Auffrey at CIDER. Today is August 27, 2019. Welcome to this special ESP Evidence Brief Cyberseminar preparatory to the SOTA15 Effective Management of Pain and Addiction Strategies to Improve Opioid Safety which will be held September 11th and 12th, 2019. This is the third of three sessions today. It is entitled Benefits and Harms of Long-term Opioid Dose Reduction or Discontinuation in Patients with Chronic Pain and will be presented by Kate Mackey with assistance by Kim Peterson. And as it’s just now the top of the hour, Kate, can I turn things over to you?

**Dr. Kate Mackey:** Sounds great. Thank you. Okay. Hello. My name is Kate Mackey. I’m a clinical investigator with the ESP here in Portland and also on the line from ESP is Kim Peterson. She’s a senior research associate located in Bend. And we both thank you and thank you on behalf of our whole team for the opportunity to present the findings of the report today. So we’ll first start out by giving you a little bit of background related to the ESP specifically and the types of evidence synthesis products that we produce. We’ll also give you some background on the 0pioid SOTA, the conference that’s coming up in a couple of weeks, as well as an overview of this topic related to [unintelligible 1:39] long term opioid findings from our review and then at the end, there’ll be time for our discussion and any questions.

We wanted to acknowledge some of our co-authors who could not be here on the line today, so Johanna Anderson, Donald Bourne, and Emilie Chen. We also wanted to acknowledge and thank our operational partners, Dr. Frank and Dr. Sandbrink, who provided input on the scope of this report as well as reviewed a draft copy.

This is our standard disclosure statement. The most important thing here is to highlight that the findings and conclusions of this report are ours alone as the authors and do not necessarily represent the views of the Department of Veterans Affairs or the U.S. Government. Therefore no statement in this article, or in this report, should be construed as an official position of the Department of Veterans Affairs. And none of us have any conflicts of interest to disclose.

So with that I’ll turn things over to Kim who will provide some more details related to our program, ESP.

Kim Peterson: Thank you, Kate. Good morning everyone. So I’m going to provide a brief overview of our program and the products that we produce, although many of you might be familiar with us, can bear with me. So the ESP is an Evidence Synthesis Group that is embedded within VA and currently funded by HSR&D. We were established in 2007. And we have a mission here, as on the slide states, of producing high quality evidence synthesis reports that we make available to clinicians, managers, and policymakers to support their important work of improving the health and healthcare of Veterans. And here on the slide is a screenshot of our website and our web address for those of you who want to visit our website to find out more about our program. Next slide, please.

So we have four Evidence Synthesis Centers located across the U.S.; one in Portland, one in LA, one in Minneapolis, and one in Durham. As well we have a Coordinating Center located in Portland where we oversee National Program Operations and ensure methodological consistency across the centers and interface with stakeholders. And also we have a group of folks there, including the two of us on the phone, that lead the Rapid Review Program which I’ll be talking about in the next few slides. And the program itself was founded by Mark Helfand and then the Coordinating Center is led by Dr. Helfand as well as Nicole Floyd whose the Deputy Director. And in terms of our qualifications, all of our centers are directed by VA Clinicians who have, in some cases, internationally renounced systematic review expertise. As well we all have close ties to the Agency for Healthcare Research and Quality Evidence Based Practice Center Program and the Cochran Collaboration. Next slide, please.

And so as part of our ongoing quality improvement efforts, we survey our operational partners about how they use our reviews three months after we complete the final reports. And this slide is summarizing or identifying the top four usages of our reports and so those include; informing, development of guidelines and performance measures, identifying the most effective services for patients, informing clinical policies, as well as in the case of this SOTA, informing direction for future research agendas. Next slide please.

Thank you. And now I’m just going to give a brief overview of the types of evidence products we offer because we do offer a variety of products. We developed several new products over the years to meet all kinds of different information needs. And as this table shows, the products that we produce range in their balance of speed, rigor, and scope. And the three indicators of rigor that we’ve listed here whether or not they fully follow all systematic review steps and whether or not they include critical appraisal of evidence and external peer review. And so in the top line there of the table is our signature product, the standard systematic review, which is really the only one that fully meets the industry gold standard in terms of standard systematic review methodology. It’s the product that we started out when we established the program in 2007 and is still is our most common product and it’s our most comprehensive product. It covers the broadest scope and uses the most methodologically rigorous processes and provides the most definitive and defensible answers. But you can see the tradeoff is it takes the longest. It typically takes about 9 to 12 months to produce. So then over the years to meet different kinds of information needs that are either more urgent, like for this SOTA, and/or that don’t require as much rigor and/or critical appraisal, we then developed some narrower and/or more abbreviated products that we can produce in shorter time frames, anywhere from two weeks to four months. And so go ahead to the next slide, please.

Thank you. And so then I wanted to draw your attention to the type of product that, or orient you to the type of product that we produced for this SOTA. And the type of report that we’re going to be presenting today is one of those more abbreviated products that we were able to produce within four months which is the Rapid Evidence Brief which we’ve highlighted here in this slide. So of our abbreviated products, it is the most rigorous in that it does, in fact, generally follow but does streamline accepted systematic review methods. And it did include critical appraisal and external peer review, but just has a narrower scope in this case, and we did streamline a few things which we will be talking about in the coming slides. So with that, I’ll go to the next slide and I think turn it back over to Kate and she’s going to take it from here.

**Dr. Kate Mackey:** Yep. Thank you, Kim. So as you know, and as Kim mentioned, this is the third report we’ve presented today and the third report that. We were asked to prepare three reports in anticipation of a conference that’s coming up in a few weeks hosted by VA HSR&D on Effective Management of Pain and Addiction Strategies to Improve Opioid Safety. So the goals of that conference are broad. And where the ESP comes in is to review the state of evidence for a specific set of key questions that were defined by the conference workgroups and try to evaluate the relevance of that evidence to VA populations.

So we prepared a report for each of the three workgroups for this SOTA and the report we’re talking about in this presentation is for work group two, Long-term Opioid Therapy and Tapering.

So this group, those on the line are well aware of we are in the midst of a evolving crisis of morbidity and mortality and misuse due to opioids. And a few years ago, VA and Department of Defense and CDC both issued guidelines recommending considering tapers of long term opioids when risks seemed to outweigh benefits in consultation with patients as we’ll talk about. And so the fact of the matter of the opioid crisis and the presence of these guidelines has created a difficult balance for a patient to, with chronic pain whose has been on long term opioid therapy as well as the providers who care for them, try to decide which would be the best path. Trying to decided potentially between negative outcomes in both manners. So potential harms from continuing long term opioids and potential benefits and harms from tapering long term opioids.

So to highlight a little bit more about what the VA, DoD, and CDC tapering guidelines recommend. So they both are very careful to emphasize the importance of shared decision making regarding long term opioid tapers as well as the importance of individualizing taper speeds. They both present gradual tapers with pauses as needed per patient requests or if clinically indicated. And very similar approaches are recommended by the American Academy of Family Physicians, the Washington State Agency Medical Director’s Group, and the Oregon Pain Guidance Clinical Advisory Group.

So despite the pretty specific and well laid out guidance sets included in the VA and CDC guidelines, there have been concerns about the implications of these guidelines related to tapers of long term opioids. And basically these concerns have arisen due to finding that some clinicians, health systems, and payers have misapplied the guidelines to impose those thresholds or impose tapers on patients. The authors of the CDC guideline recently published a perspective piece where they highlighted some of these concerns and tried to clarify the intent of the CDC guidelines and criticized inflexible application of recommended dosage and duration thresholds in policies that encourage hard limits and abrupt tapering of drug dosages resulting in sudden opioid discontinuation or dismissal of patients from a physician’s practice. Similarly a few months ago, the FDA issued a statement highlighting anecdotal evidence of harms related to opioid tapers stating, “Recently, the FDA has received reports of serious harm including serious withdrawal symptoms, uncontrolled pain and suicide in patients who are physically dependent on opioid pain medications when these medications are suddenly discontinued or when the dose is reduced too quickly often without adequate patient communication, follow-up, or support. “

And so those concerns raised by the authors of the CDC guideline and the FDA really highlight the importance of understanding what patient outcomes are following tapers of long term opioid therapy. The best evidence that we’ve had comes from a review by Dr. Frank who is one of our operational partners and colleagues, many of whom may be on the line as well. Dr. Frank and colleagues published a systematic review in 2017 that was focused on looking at the effectiveness of different tapering strategies but also included an analysis of patient outcome following tapering. So the Frank review included four studies of patient outcomes. They found that most studies were fair or poor quality. I think there was only one study in this group that was deemed good quality. And overall, they found inconclusive evidence on the impact of LTOT tapers on pain severity, pain related function, quality of life, withdrawal symptoms, substance abuse, and adverse effects. And those are the six outcomes that they evaluated.

So the goal our review was to update, build on the review by Frank and colleagues to synthesize the evidence on opioid dose reduction and discontinuation for a broader range of outcomes and with an emphasis on the evidence most relevant and applicable to the VA population. We also aimed to identify evidence gaps which is particularly relevant for the goals of the opioid SOTA conference coming up in a few weeks.

So here are a link to the text of our full report which you probably also have in your email somewhere.

So we examined two key questions that we developed in partnership with our operational partners. So key question one; among patients prescribed long-term opioid therapy for chronic pain, what are the benefits and harms of opioid dose reduction or discontinuation? And then key question 2; do these benefits and harms vary by patient characteristics, patient engagement in tapering or, in other words, whether or not the taper was initiated by the patient or the clinician or whether it was considered voluntary or involuntary, the specifics of the opioid regimen, and the characteristics of the tapering process itself, whether or not it was fast or slow or there were adjunctive medications or other co-intervention.

Here are our eligibility criteria. So we included studies of adults with chronic pain prescribed long term opioids commonly defined as greater than three months. We excluded patients receiving palliative care or treatment for cancer related pain or undergoing surgery. We looked at any interventions that involved dose reduction or discontinuation. In contrast to the review by Frank and colleagues, we had a narrower scope in that we only included studies where the intervention specifically was to reduce or discontinue opioid doses. We did not include studies that were of a different kind of pain management intervention that may have also have had the bi-products of patients reducing their opioids. But that’s a difference between our two reviews. In terms of outcomes, so most of these were also included in the Frank review where we expanded, we included; patient satisfaction, healthcare utilization and then, although the Frank review looked for any adverse outcomes, we specifically looked for opioid overdose and suicidal ideation and suicidal self-directed violence.

So just running through our methods which are standard. And if you’ve been following along all morning, you’ve heard this run through before. So we searched from the end search date of the Frank review which was the beginning of January 2017 through March to capture new studies that were published since that review. We used our eligibility criteria to determine which studies we would include. We extracted data including outcomes from interest from all of those studies. We performed critical appraisal which we’ll discuss in a couple of slides using standardized tools. In this case, we used grade methodology. In term of our internal quality control, the assessments including data abstraction were first completed by one reviewer and then checked by at least one other person. Disagreements were resolved by consensus. And we had a draft report that underwent peer review that included experts outside of the VA and their feedback on our draft and our responses to their feedback are publicly available. They are in our supplemental materials which are also online.

So the Frank review used grade criteria to evaluate the quality of studies. And so we took their lead and also used the grade criteria to evaluate the body of evidence as a whole. So these criteria are very similar to other standard tools that take into account methodologic limitations of the study, so how different methods may introduce different sources of bias. These criteria also include precision, consistency, and directness, and result in scores ranging from high to very low. So the findings of the Frank review were in the very low category, just as a frame of reference.

So here’s our study selection flow sheet. As I mentioned, we searched from the end search date of the Frank review to look for new studies. We also included all of the studies that looked at patient outcomes from the Frank review and because we were looking for additional outcomes from those studies. So that resulted in 45 articles that met our inclusion criteria; the systematic review which is the one by Frank and colleagues, thirty four of the studies that were included in that systematic review and 10 new studies.

We also performed another layer of prioritizing the evidence, especially in the context of a rapid review. We found that this is helpful to provide the highest quality and most relevant evident synthesis to stakeholders. So our first priority is looking at any studies conducted in the VA setting. So secondary to that, we looked at studies that were outside of the VA but had sufficiently described their population and intervention so that we could evaluate how applicable they would be to the VA. And then, for this report, we also included any study that, or prioritized, any study that discussed serious harms of tapering regardless of setting or how well they described the population or the intervention because of our particular interest in evaluating harms including overdose and suicide. And then it’s the remainder of studies that we included in our report and abstracted data for but did not prioritize in terms of our evidence synthesis because we did not think they were as applicable to the VA.

So that left us with 15 prioritized studies which included two randomized control trials, two observational studies with a control group, 11 observational studies without a control group. And the studies that we included, but not prioritized for our synthesis, had low applicability to the VA or, as I mentioned, included patients or interventions that were not well enough described so that we could say one way or the other.

So this slide just gives you a snapshot of the kinds of studies that we found. About a third were conducted in VA settings. Overall in terms of chronic pain conditions a patient had musculoskeletal concerns were definitely the most prevalent with back pain being common. Most of the tapers included in these studies were voluntary and I’ll say more about that later. And most of them also had a fast taper speed and I’ll also say more about that later. And we defined fast as less than a month.

So going back to our key questions and getting into the results for key question one; so among patients prescribed long-term opioid therapy what are the benefits and harms of opioid dose reduction or discontinuation?

So this slide provides a summary of our results and, don’t worry, I am not planning to go through this line by line. I actually included this, this table is also in the text of our report. But really I wanted to include it because it highlights all the white space, all of the gaps where some of these important outcomes were not captured by these studies. So as you can see, several studies evaluated the impact of tapers on pain severity and pain related function. But really a minority listed adverse advents following tapers. And we didn’t identify one study that examined the full range of patient outcomes following tapers. So in terms of kind of an ideal study, what we would be looking for, we didn’t really find a study that matched that.

So getting into the results in a little bit more detail. We noticed a distinction between tapering and interventions that we considered higher intensity versus tapering and interventions that we considered medium or low or studies where the tapering intervention really wasn’t described at all. So there were six studies in a total of 15 prioritized studies that featured high intensity intervention and, as an example of what we mean by that, here’s a description from one of these studies which is from the Cleveland Clinic Outpatient Interdisciplinary Chronic Pain Rehab Program. So this program involves participation for most of the day, Monday through Friday, includes daily medical management, individual and group psychotherapy, cognitive behavioral group interventions, physical and occupational therapy, substance use education, weaning from habituating medications, and optional monthly aftercare. So quite an intensive study. And this was, again, six out of our 15 studies. So interventions like this took place at the Cleveland Clinic, The Mayo Clinic. There was one from the VA program in Florida. And as this graph demonstrates, the outcomes are pretty good. So these interventions all occurred over a several weeks timeframe ranging from three to five weeks. And outcomes related to pain severity are positive showing improvement in most cases as well as improvement in pain related function and improvement in scores related to depression and anxiety. Importantly none of these studies captured or described or reported adverse events associated with tapering.

In contrast, the remainder of the studies that we included in those 15 prioritized studies had lower intensity interventions. So as an example of moderate intervention, there were two randomized control trials that were both embedded in multidisciplinary pain clinics. One involved optimizing opioid medications prior to a scheduled taper and the other involved a taper paired with pretty extensive psychosocial support, so meeting with a physician assistant who was trained in talking to patients about self-management skills. And that intervention included other components as well but also included meeting with this physician assistant weekly for 18 visits, so fairly intense, more than you would expect in a primary care setting. And then an example of a low intensity intervention, we found one study that discussed an individualized taper that guided by a clinician where the patient also received a self-help book. And then in six of the 15 studies, they described dose reduction and discontinuation but did not describe a specific intervention. And many of those studies were related to opioid harm which is why we included them in our prioritized studies. You can see in terms of the outcomes not quite as impressive in terms of pain severity. So studies still reported improvement or no change but these outcomes were not fully evaluated by most studies and also a minority of these studies reported on any adverse event.

And then we wanted to also highlight an important caveat at interpreting these results in general for both the high intensity and the lower intensity studies. That studies used common measures of pain severity so, for example, the pain numerical rating scale, and reported on mean changes. And so it’s really hard to know, based on information like that, how clinically meaningful those changes were to a patient. So for example, if someone average pain score went from nine to three following an intervention that is encouraging, but we don’t know whether that was a meaningful difference for the patient or not. Also there’s a lot of, as you all know, patients can have fears about tapering of opioids including the concern for having rebound pain and so using these kind of scales doesn’t necessarily get at that. So for example, none of the studies reported what proportion of patients experienced significant enough rebound pain that they would have to have a change in their management plan. So that’s an important limitation of the existing evidence.

So the next few slides discuss specifically some of the potential adverse events associated with tapers. So for the impact of tapers on substance use, really the evidence is unclear as studies did not directly examine this outcome. So the best study we have on this topic was recently published. It’s a study by Mark and colleagues based on Medicaid claims data in Vermont. And these authors look at a subset of patients who were on hiatus opioids above 120 morphine equivalent and had their doses discontinued. Prior to discontinuation, more than half of the patients had a diagnosis of substance use disorder. And this study was primarily looking at healthcare utilization and reasons for ED visits after opioid discontinuation. And found that almost half of patients had an ED visit or hospitalization due to opioid poisoning or substance use disorder. Interestingly in this study, less than 1% of patients were transitioned onto an opioid use disorder medication. So I think, reflecting on this study, I think it actually may raise more questions than it answers. But it does suggest that a significant of portion of patients who have been receiving or who may be discontinued from their long term opioids, have underlying substance use and that that could certainly translate into more ED visits. The study does not describe reasons why opioids were tapered so we can’t exclude reverse causation. So for example, if a clinician is worried about a patient misusing their opioids or considers the patient to be at high risk of overdose that may have been the reason for discontinuation. So we are not able to answer those kinds of questions with this study.

So moving on to the impact of tapers on opioid overdose. Really the same limitations, the evidence is unclear as few studies have examined this outcome. The best evidence that we have comes from a 2019 large retrospective study by Von Korff and colleagues from Washington state looking at opioid overdose rates following different phases of a risk reduction initiative comparing rates of overdose among patients who were followed in Washington’s Group Health practice to patients who were followed at Group Health contracted community clinics. And the two phases of the dose reduction initiative, the first phase involved a effort at dose reduction and the second phase involved increase use of risk mitigation like opioid drug screens and prescription drug monitoring program. And so this study found that overdose rates decreased by 17% within the intervention group, so within the Group Health practice, after the first phase that was aimed at dose reduction but was not significantly different when compared to the control groups. So there was a within group difference but there wasn’t a between group difference. And overall the results of this study we found to be difficult to interpret the significance of and that the best we can say is that this study provides inconsistent support that reducing opioid doses leads to lower overdose rates. And again, similar to the previous study, this study did not capture the potential for reverse causation that clinicians were worried about overdose risk among patients and, therefore, discontinued opioids. We’re not able to know that from the study.

And then looking at the impact of tapers on suicide risk, really the same category for the other serious adverse outcomes. The evidence is unclear as very few studies have examined this outcome. So the best evidence comes from a 2017 study by several colleagues here, some of whom may be on the line, that looked retrospectively using chart reviews at a subset of patients who had substance use disorder compared to match control who underwent mostly clinician initiated tapers, so 75%, due to apparent behaviors such as unexpected results on urine drug screens or prescription drug monitoring program. And so 47 of these patients had new onset suicidal ideation and 12 had suicidal self-directed violence in the year following opioid discontinuation. And the authors found that having baseline PTSD or psychotic disorders were associated with a higher risk of suicidal ideation and suicidal self-directed violence. This is really the only study that has delved into the association between tapers and suicide risk. It has important limitations, however, including that almost certainly these are underestimates of the rates of suicidal ideation and suicidal self-directed violence as the data was obtained by chart review only. So any information not in the chart we wouldn’t know about. Patients who died in the year after opioid discontinuation were excluded from analysis. So if a patient actually died by suicide they wouldn’t have been captured in this, and excluded patients who had no contact in the year following discontinuation. So again, that would have probably missed several people.

So moving on to our second key question asking whether these benefits and harms of opioid dose reduction or discontinuation vary by any of these characteristics.

And, unfortunately, we found very limited evidence to be able to address this key question. So what we would have been looking for would have been a study that provided an analysis by sub-groups. So saying that within this intervention this subset of patients was more or less likely to have this outcome compared to others. And we really didn’t see that except, for example, the study that showed that patients with baseline PTSD, or psychiatric disorders, had a higher risk of suicidal ideation or suicidal self-directed violence. Otherwise we were not able to find subgroup analyses to answer this key question. So that’s an important evidence gap.

So in terms of a discussion and a summary so far, so we found that pain severity and function may improve with voluntary intensive pain management interventions that incorporate opiate tapering. So those are all of the interventions along the lines of the Cleveland Clinic, one that I highlighted, but may not change with less intensive interventions. However, our confidence in these findings is low and additional evidence is needed before drawing stronger conclusions. And really findings for the other outcomes remain inconclusive though very low quality using the grade criteria. And we know the least about outcomes with clinician initiated and in involuntary tapers included outcomes for patients suspected of opioid misuse.

So in terms of our evidence gaps, there are many which suggests areas for future research. So we suggest focusing future research, or a big evidence gap is not knowing the rates of serious adverse events following tapers including overdose and suicide. Also, not clearly knowing the rates of newly diagnosed opioid use disorder following tapers. I didn’t get into this very much in the slides but do more so in the report, the discussion of the concept of complex persistent opioid dependence and how this factors into outcomes following tapers. And then another gap is knowing which specific patient and intervention characteristics are associated with improved outcome and which are associated with more harm and how these outcomes might differ between different tapering strategies including whether the taper is voluntary and patient initiated or mandated.

So to summarize our limitations starting with the limitations of the evidence base itself. So these are mostly observational studies without a control group. So those have an inherit risk of bias. There’s unclear fidelity to interventions meaning that we didn’t always know if the patients received the interventions as they were designed to be received. There is inadequate reporting or unclear handling of missing data in some studies. And as Kim highlighted, this is a rapid review so we streamlined some of our methods and that might have resulted in missing eligible studies or study data.

So in terms of our conclusion. We overall concluded that the evidence is inadequate to fully weigh the balance of benefits and harms of tapers for chronic, chronic pain against the benefits and harms, or I’m sorry, inadequate to fully weigh the balance of benefits and harms of continuing long term opioid therapy for chronic pain against the benefits and harms of tapering mostly because we lack information about tapering harm.

There’s obviously much more to say but in the constraints of this Cyberseminar we will leave it there and see if there is anyone listening who would like to ask any questions.

**Rob:** There are no questions pending at this time. Joe Frank did attend but he explained to me that he had to leave at 2:25 to get back to his primary care clinic.

**Dr. Kate Mackey:** Okay.

**Rob:**  So there are no comments or questions at this time. Perhaps if anybody has closing comments? You know you might want to make closing comments while we wait for potential questions but given the lack of questions this morning, probably not going to get any because people have conveyed to me that both of the previous webinars were incredibly jam packed full of information. I do have a couple of comments. Somebody said thank you very much. And another person said, no question, but nice review, thanks. And another person said we have a lot to do.

**Dr. Kate Mackey:** Thank you. Thank you for the feedback and, yes, there is a lot of detail related to this report. And this is a very complex topic in general so there is a lot more discussion in the report itself. And I’m sure that those attending the conference in a few weeks will be able to delve in and think of more questions. And anyone listening is welcome to contact me in the meantime. And I’m also planning to be there at the conference so if there are any questions specific to the report, I’d be happy to talk about them at that time too.

**Rob:** Thank you very much, Kate. And thank you, Kim. With that, I’ll just go ahead and close the webinar.

**Kim Peterson:** Thank you, Rob.

**Dr. Kate Mackey:** Thank you.

[END OF AUDIO]