COCA Call: Opioid Analgesics: The Epidemiology of Misuse and Advice on Prescribing.

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Speakers:

Dr. Len Paulozzi, Medical Epidemiologist, Division of Unintentional Injury Prevention (CDC)

Dr. David Tauben, Clinical Associate Professor, University of Washington, School of Medicine

Coordinator: Welcome and thank you for standing by. At this time all participants are in a listen-only mode. During the question and answer session please press star 1 on your touchtone. Today's conference is being recorded; if you have any objections, you may disconnect at this time.

Now I will turn the meeting over to Ms. Loretta Jackson-Brown. Thank you, ma'am.

Loretta Jackson-Brown: Thank you, (Ana Lee). Good afternoon. I'm Loretta Jackson-Brown and I am representing the Clinician Outreach and Communication Activity, COCA, with the Emergency Communication System at the Centers for Disease Control and Prevention. I am delighted to welcome you to today's COCA conference call, Opioid Analgesics: The Epidemiology of Misuse and Advice on Prescribing.

We are pleased to have Dr. Len Paulozzi, Medical Epidemiologist, National Center for Injury Prevention and Control at Centers for Disease Control and Prevention, and Dr. David Tauben, Clinical Associate Professor, University of Washington, School of Medicine, here with us today to discuss the increased

rate of opioid overdose and the role clinicians play in preventing these overdoses.

During today's call, you will hear the presenters referring to slides in their PowerPoint presentation. The PowerPoint slide set is available from our COCA Web site at emergency.cdc.gov/coca. Click on conference calls. The slide set can be found under the call in number and call passcode.

The objectives for today's call are that participants will be able to discuss the prevalence of misuse of prescription opioid analgesics, identify factors that increase the risk of overdosing on opioid analgesics, discuss precautions in prescribing opioids for chronic non-cancer pain, describe opioid responsiveness limitations, compare and contrast morphine equivalent dose for single and multi-drug treatments, and explain the components of a time-limited and functional outcome directed opioid trial.

Following the presentation, you will have an opportunity to ask our presenters questions. Dialing star 1 will put you into the queue for questions.

In compliance with continuing education requirements, all presenters must disclose any financial or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters, as well as any use of an unlabeled product or products under investigational use.

This presentation will not include a discussion of the unlabeled use of a product or of products under investigational use, with the exception of incidental references to antidepressant and antiepileptic drugs, many of which

are not labeled for use as analgesics but are widely used with well-established evidence of efficacy.

CDC, our planners, and our presenters wish to disclose that they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters. There is no commercial support for this presentation.

Our first presenter, Dr. Paulozzi, is a medical epidemiologist for the Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, CDC. Dr. Paulozzi obtained a doctorate of medicine from Ohio State University and a master's in public health from the University of Washington. Since 2005, his interest of concentration has been drug overdoses, especially those due to prescription drugs.

Dr. Paulozzi has authored and coauthored more than 80 publications during his 27 years working in public health. He has testified at Senate and House hearings related to prescription drug use and his work is frequently cited in both the popular press and scientific literature.

Our second presenter, Dr. Tauben, is a Clinical Associate Professor, Medicine, Anesthesia & Pain Medicine at University of Washington, School of Medicine, Seattle, Washington. He is board certified in both internal medicine and pain medicine. He is the Director of Medical Student Education and Pain Medicine at the University of Washington and jointly appointed in the Department of Medicine and Anesthesia & Pain Medicine.

As a founding member of the State of Washington Agency Medical Directors' panel of medical experts developing opioid prescription guidelines for the state, he serves as an expert for state agencies and legislative bodies involved in public policy regarding pain medicine practice and standards.

A faculty leader at the University of Washington, Center for Pain Relief, his team was the recipient of the American Pain Society's 2010 Center for Excellence Award. He is currently implementing a four-year integrated medical student curriculum in pain medicine and a primary care pain consultation telemedicine project in Washington, Wyoming, Alaska, Montana, and Idaho.

If you're following along on the slides, you should be on Slide 6. Again, the PowerPoint slide set is available from our COCA Web site at emergency.cdc.gov/coca.

At this time, please welcome our first presenter, Dr. Paulozzi.

Dr. Len Paulozzi: Thank you, Loretta. And good morning to those of you on the Western part of the country and good afternoon to those of you in the East. Thank you for joining us today.

I'm going to talk about the epidemiology of misuse of opioid analgesics. Basically my presentation will have three parts, shown on Slide 7: The background on the problem; the demographic risk factors for opioid abuse; and behavioral risk factors for opioid abuse.

On Slide 8, I open with this epi curve showing you the unintentional drug overdose death rate in the United States between 1970 and 2007. The Y axis shows the death rate per 100,000 people. In 1970 the overdose rate was about 1 per 100,000. In 1990 it had risen to 2 per 100,000 largely because of heroin and crack cocaine. But by 2007 the rate had increased to more than 9 per 100,000; and this is the point where we are in this pharmaco-epidemic today. In 2007 almost 28,000 deaths occurred from unintentional drug overdoses in the United States and that makes drug overdoses second only to motor vehicle crashes as a leading cause of injury death in the United States.

On Slide 9 I try to break down this rising curve in drug overdoses from 1999 through 2007 for you. The three major classes of drugs shown on this figure include the opioid analgesics in orange, cocaine in the middle line, and heroin in green along the bottom. As you can see, back in 1999 the opioid analgesics were involved in fewer of these unintentional drug overdose deaths than cocaine. But what happened since 1999 was a dramatic rise in the number of deaths where the death certificate cited opioid analgesics, a somewhat less increase in the number of deaths where cocaine was cited, and relatively flat numbers over this time span for heroin. Note that these figures are conservative numbers because in many drug overdose deaths, the death certificate does not specify the kind of drug that is involved.

On Slide 10, I show again the same line for opioid analgesics as in Slide 9, but here it's paired up with data from the Drug Enforcement Administration about per capita sales of opioid analgesics in the United States in morphine milligram equivalents per person. So generally as the deaths have risen from 1999 forward, there has been a parallel increase in opioid sales. In 1997 approximately 100 morphine milligram equivalents per person were

distributed in the United States and by 2007, just eight years later, that use had increased to about 700 morphine milligram equivalents per person. And that's the latest data available today.

On Slide 11 I just wanted to give you some background in this - in the epidemiology of opioid misuse. Sometimes the terminology is different from what you may use in clinical practice. But when people talk about prescription drug abuse, it - generally they mean something like the NIDA definition shown on Slide 11, taking a prescription medication that is not prescribed or taking it for reasons or in dosages other than prescribed.

There is another phrase that's commonly used, and I will use it today, and that's called medi - nonmedical use or misuse and it's defined by the Substance Abuse and Mental Health Services Administration in its surveys as use of medications without a prescription of one's own or simply for the experience or feeling the drug causes.

In this particular presentation, going on to Slide 12, I am going to show you some emergency department data, ED data and survey data, both from the Substance Abuse and Mental Health Services Administration, and there the non-medical use definition used by SAMHSA applies.

I'm also going to show you mortality data, like that in the first few slides, but in mortality data it's more difficult to use formal definitions of abuse or misuse. The information on the death certificates often is - usually is inadequate to know the reason - the person's reason for taking the drugs or the circumstances. So drug overdose deaths on death certificates might include people taking too much for purely medical reasons, either without a

prescription or because of mistakes in prescribing; it also may include purely unintentional ingestion. We just don't know the reason for most of the deaths.

However, the working assumption with most of the mortality data today is that most of the deaths will represent some form of nonmedical use of the drugs. And really for two reasons because deaths from unintentional ingestion or taking prescribed drugs as directed is relatively uncommon, it happens, but it's a small fraction of the deaths, and also because we have some substantial evidence that the people dying of drug overdose related deaths involving opioid analgesics were involved in non-medical use. And I'll show you that data in a minute.

Slide 13 begins a section of my talk on the demographic risk factors. And here I try to show what the sex ratio is to give you a sense of sex as a risk factor. In general, if you look at unintentional drug poisoning or overdose deaths, the first row of the table on Slide 13, in 2007 our vital statistics system shows that there's almost two male deaths for every one female death. If you look just at the opioid analgesic related drug overdose deaths in 2006, it's 1.8 male deaths for every female death.

However, when you start to look at the non-fatal outcomes, such as emergency department visits for non-medical use of opioids, and this is 2008 data from the Drug Abuse Warning Network or DAWN of SAMHSA, the male and - male/female ratio is equal. You know, the females are at equal risk of appearing in emergency departments because of non-medical use of opioid analgesics.

Similarly, the non-medical use of prescription pain relievers in the past month from the SAMHSA National Survey of Drug Use and Health in 2008 shows that the male and female rates were comparable with a slight excess among males.

And finally, if you look at the regular use of opioid analgesics in various surveys where people self-report, opioid analgesics are more likely to be used by women than by men.

Going on to Slide 14 and starting into the issue of age, age relationship to this problem varies depending on the outcome you're looking at. Slide 14 shows poisoning deaths involving opioid analgesics from a 2009 report from the National Center for Health Statistics. And this shows that the highest rate of such deaths was in the 45 to 54 years age group. Relatively few deaths occurred among children and among people over the age of 65.

However, if you move to Slide 15, which looks at age-specific rates for emergency department visits for nonmedical use of opioid analgesics in the United States in 2008, the pattern is somewhat different. The highest rates, about 200 per 100,000, were - occurred in the 21 to 24 years age group. So the people in their 20s had - are more likely to appear than any other age group in emergency departments for non-medical use; in contrast to the fatality data, which showed older people in their 40s and 50s being in - at greatest risk when deaths involve opioid analgesics.

And finally, on Slide 16, this is survey data from the National Survey on Drug Use and Health, showing that when you ask people about their non-medical use of opioid analgesics, about 12% of those in the 18- to 25-year age group

reported that they had so used opioids in the past year. And that age group had a higher rate of this nonmedical use than older people. Rates tend to decline after the 20s as people aged.

On Slide 17, looking at the issue of race/ethnicity, the white bars indicate drug deaths - drug overdose deaths per 100,000; so these are all drugs involved. The highest rates for any drugs were 13.5 per 100,000 in non-Hispanic whites, the next highest rate was in American Indian, and Alaskan Natives, and non-Hispanic blacks had a rate of 10.9. Hispanics and Asians had lower rates.

When you look at data just about overdose deaths involving opioid analgesics from the NCHS report, again non-Hispanic whites have the highest rates, and they are substantially higher than the rates for blacks or Hispanics. And data is not published for rates of opioid analgesics death in American Indians or Asians to date.

Slide 18 looks at the geographic variation by state in - this is death rates for drug overdoses that were unintentional or of undetermined intent in 2007. Here the highest rates shown in the darkest color were found in Appalachian states and in Southwestern states with the highest rate in the country being in the State of West Virginia and the second highest rate being in the State of New Mexico.

And you can compare that to Slide 19, which is taken from the NCHS data brief, and this shows age-adjusted death rates for poisoning involving opioid analgesics, again, data from death certificates. And there's similarities to the previous map. Note here that the lowest rates are in the medium gray color, so the lowest rates are in large urban states like New York, Texas, and California

and in some of the states in the upper Midwest such as Iowa, Minnesota, Nebraska, and so on. This is similar to the pattern seen in the overall death-rate map on Slide 18.

On Slide 20 there is some information that may help to explain the state-to-state variation. This is data looking at drug overdose death rates by drug type and by urbanization. We looked at the data by county and categorized the counties into six categories ranging from the most metropolitan and large central metro counties, which are shown on the left of the figure, all the way over to the most rural counties, which are called non-core, non-metropolitan counties to the right.

What you can see is that the rates shown in orange for opioid analgesics actually somewhat higher in the non-metropolitan counties than in the metropolitan counties. For heroin, shown in green, the highest rates are in the large central metropolitan counties. We traditionally associate rates of illicit drug overdose with large metropolitan areas, but the pattern is different with opioid analgesics with higher rates in the smallest and most rural of communities.

Slide 21 moves from the demographic to the behavioral risk factors; 21 shows some characteristics of unintentional pharmaceutical overdose deaths in West Virginia in 2006. This gets into why I said earlier that we think that there's substantial evidence for misuse in - of prescription drugs involved in these deaths. These are pharmaceutical overdose deaths, and this is data from the State Medical Examiner in West Virginia. Among these 295 deaths, about 78% had some sort of history of substance abuse; 43% had some other form of mental illness; 63%, almost 2 out of 3 deaths, had one or more prescription

drugs involved in the death for which they had no prescription in the State's prescription drug monitoring program.

About a 1/5 of the deaths involved a non-medical route of administration, such as injection or snorting the drug; in about 1/5 of the deaths, the decedents had seen five or more prescribers for controlled substances in the previous year; and about 16-17% had a previous overdose. All told, about 95% of the decedents had one of these last four risk factors shown on this table.

Compare that to Slide 22 which is more recent data presented by Dr. Bill Lanier at the 2010 Epidemic Intelligence Service Conference at the CDC this past spring. This is a study of unintentional opioid overdose deaths in the State of Utah; 278 deaths were involved. And the general feeling before doing this study among people in the states was that substance abuse has a smaller role in the Utah population than it might have in some other states.

The results were, though, that there was a history of substance abuse in about 61% of the decedents and there were signs of some form of medic - non-medical use in just about 1/2 of the decedents. By nonmedical use, they meant any opioid involved without a prescription, which is shown there as 37%, but also taking more than prescribed, visiting more than one doctor for controlled substances, and using for non-pain reasons. All totaled, those signs of nonmedical use was present in 51%.

In addition, over 80% have a history of some form of chronic pain and about 50% had a history of some form of mental illness that was diagnosed by a healthcare provider.

In Slide 23, this is data from living patients rather than people who have died of overdoses. This is from the State of Maine from 2006; a study by White. And the authors of this study looked for the risk of opioid abuse measured in terms of claims for overdose or substance abuse in their insurance data and they looked at risk factors for having such a claim for opioid abuse.

They found that use of three or more pharmacies for opioids doubled the risk after adjustment for having a claim for opioid abuse. They found that one or more early refills of an opioid prescription dramatically increased the risk to 6.5. Also a 50% or more increase in opioid dosage per month over two consecutive months was a significant risk factor as was 12 or more opioid prescriptions during this 12-month period; and as was a mental health history, as shown in the fatalities studies, but in this case a depression diagnosis was a significant risk factor for opioid abuse.

And lastly, we have some limited data on Slide 24 on dosages received by people who overdosed in unpublished data from the Washington Medicaid program. They found that people who died of opioid overdoses had been prescribed a mean of more than 180 morphine milligram equivalents per day.

In a published study by Dunn in 2010, and this is an HMO population, and the overdose risk ratio increased in a graded fashion with increasing prescribed daily dose. So if the referent group was - had an odds ratio of one, people who were prescribed fewer than 20 morphine milligram equivalents per day, the risk of a serious overdose, not necessarily a fatal one, increased all the way up to 8.9 among people who have been prescribed 100 or more morphine milligram equivalents per day.

So in summary, my last slide, number 25, the risk we saw for opioid misuse, as measured by various outcomes, seems to be equal for women and greater for young people, under age 26, if you're looking at the non-fatal outcomes; but for the fatal outcomes men and the middle-aged groups seem to dominate those statistics. Non-Hispanic whites seem to be at highest risk for opioid misuse. Risk of misuse of the drug might be increased with dosage. It might be greater when dosage is escalated rapidly, with greater number of prescriptions, and with evidence of doctor and/or pharmacy shopping. Mental illness and history of chronic pain might also be risk factors for opioid misuse.

Thank you very much.

Loretta Jackson-Brown: Thank you, Dr. Paulozzi. Please welcome our next presenter, Dr. Tauben.

Dr. David Tauben: Hello. Good morning. I'm just getting online here. Good morning to those on the West Coast, where I am, and good afternoon on the East Coast. And I'm honored to be able to contribute to this discussion today. As you can see that the data just generated and presented by Dr. Paulozzi is compelling and part of the reasons we here in Washington State are taking this very seriously.

And my hope today is, as we can see on 28, my objectives, is that how we as providers can offer our patients the safest way to manage their prescriptions and understand limits to opioid responsiveness so we don't end up on the default option, which is a patient coming in and then raising the dose of opioids, which we can see is one of the leading causes of accidental overdoses.

And offered the listeners an opportunity to either do what we call here in Washington State the morphine equivalent dose or the MED or as described by Dr. Paulozzi, the MME is another term, in other words, converting all the opioids into a - kind of a lingua franca where everyone is talking about the same numbers.

And then finally, and very importantly, how we as providers can determine the correct dose for those patients who may legitimately on a medical basis and on best clinical practice require long-term opioids for management of their chronic pain condition.

One Slide 29 I will begin by speaking to Dr. John Loeser, one of the professors here at the University of Washington who - and one of the founders in the field of pain medicine and research, his famous onion, which gives us an understanding again of what domains we're managing when we take care of a patient in pain, and when we're dealing with opiates how complicated this can be because, generally speaking, we're looking at the nociception when we're dealing with drugs. But we can often overlook the outside layers of the onion, the pain behaviors that we see, and the suffering that patients will present with and then their description of pain.

And the challenge as a provider is to be able to work through these onion skins and to get down to pain without adversely interfering with patients' function. So over the years since this onion was originally presented in the 60s, the many decades, we have a bit more complicated view of pain. And I've broken that out on Slide 30, where the bio-psychosocial domains are tabulated in my version of the injury or disease in the bottom left and we add opiates, of

course, to try to affect the metabolism and the biogenetic events that occur when we add opiates as a pharmacological agent.

And we have to remember that when we add opiates to a patient's problem, we're affecting a variety of other domains, their personality, we're affecting their beliefs that perhaps opiates are the solution to their problem, their life history, the addiction/abuse issues that were talked about, past history, their expectations again of their future life on or off opiates, and then certainly affecting their interpersonal domains and other relevant factors that are very important to be obtained in the patient history.

On Slide 31, Roz Chast entertains us in a New Yorker magazine cartoon from years ago via a patient who might often present -- she's referring to National Everything Awareness day. This just really describes an anxious patient who has lots of things on her mind. And I circled there the back pain domain, which is typically what she would be presenting to her doctor, not speaking about these other concerns that they may be relevant.

And if we take that patient and use a tool that we're using here in the clinic as we can see on Slide 32, which is one of the versions of a intake evaluation I'll speak a little bit about in a future slide, this is perhaps the way the patient may report a pain diagram. Again, speaking to the importance of using tools to be able to recognize patients for whom opiates may not be the remedy.

And I would state, for instance, to the medical students that I teach regularly that this is exactly a patient for whom opiates would not be appropriate. And if the patient returned the next visit saying her pain was worse that this would be another example of someone for whom you would not raise the dose.

And you can see I circled there for your information that this woman has had this problem for ten years. And what's interesting, in the top right corner, is what she has tried, basically everything, and that everything has been identified as side effects. But she tells you that opiates have helped her. So what do we do? How do we handle this kind of problem?

And so the first question I ask is what are opiates going to do for our patients? And this is my summary I've constructed from an exhaustive literature review and my years of clinical experience is that we can really expect typically a 30% response from opiates. There's a large variety of data out there depending on how the study is conducted whether it's a med analysis or a specific randomized trial, of which there are very few. But the response rate for opiates is at best 50%. It's similar to the response that we often get and expect to get with tricyclic antidepressant drugs in the management of pain or antiepileptic drugs, again, a 30 to 50% group.

We know - actually a recent publication this past month in the New England Journal of Medicine identified the addition of acupuncture to traditional medical techniques will add another 10% of response. And then cognitive behavioral therapy, mindfulness training, and the other non-pharmacological domains, you can see is a very potent additive; in fact, may stand alone as an effective therapy. And just improving physical fitness in a patient, there are a variety of available literature, it will, again, provide 30 to 60% improvement.

So if we're expecting - and if our patients, more importantly, are expecting a dramatic improvement in the opioid response, they will be disappointed and

the tendency will be to dose escalate and get into these very high MEDs that are associated with that adverse outcome.

On Slide 34, I'm speaking now to the value of using measurement tools in order to assess. Now we've heard from Dr. Paulozzi how important the psychiatric domains are in terms of recognizing the adverse effects associated with opiates, that a proper psychiatric and psychological monitoring needs to be put into effect, that we need as providers to continuously monitor physical function in response to all of our rehabilitative efforts, and in particular our prescription - prescribing efforts, and as we also saw that a history of drug abuse or active drug misuse or substance abuse needs to monitored in an aggressive way.

We also know, as seen on Slide 35, this is work that's been conducted here at the University of Washington, largely by Dennis Turk and his research group, that there - in the management of patients in chronic pain, six treatment domains that prove to be very relevant in making our assessments. These are as listed: pain intensity, in other words the number the patient reports their pain or their visual analog scale report; an indication of physical functioning; assessment of their emotional functioning; the patient's perception of whether they've had global improvement, this speaks somewhat to their view of optimism and a sense that they have a chance of getting well and that one's prescriptive or the non-pharmacological treatments are having an effect; monitoring symptoms of the problem, the presenting problem, as well as adverse effects; and importantly, what they're doing in terms of compliance or adherence.

And so on Slide 36, I've broken out some of the ways we can and the available tools that may be available to providers to provide this evidence-based assessment. First we need to ask the - this is just a vital sign, what the pain intensity is.

We need to identify functional capacity that the patient has before we start an opioid trial and then afterwards. We can obtain this by just getting self-reported goals, which often are unreliable and typically require some additional objective monitoring such as a significant other or other reports. The amount of pain interference in one's life. Use of a tool such as the Roland-Morris, I'll speak to that in a few minutes, which is a very useful sequential tool that can be offered at first visit and then at subsequent follow-up visits so one can quantify the improvement in functional capacity.

Mood measurement, critical and very important to monitor one's patients, those particularly on opiates, recalling back the number of domains that opiates will affect when - on the earlier slide that we could have a fairly negative affect on management of depression. We may alleviate a patient's anxiety by generating a narcotized state, but if we're looking to reduce nociception we - I would straight quite - state quite strongly are not looking to manage patient's mood primarily by using our opiates.

So we want to make certain we're not having an adverse effect, so we can use a variety of measures, the CESD-10, the PHQ-9, or a GAD-7, or whatever assess - screening tool one may be interested in and have available in their office.

Addiction risks, widely available is a number of tools and I've listed several here, the ORT, the COMM, the SOAPP-R, the AUDIT, or just the old-fashioned CAGE inventory that's adjusted for other substances. These tools take just minutes to administer and can be offered to patients prior to their visit by one's staff or even offered by the provider at the time of the visit.

And then urine drug testing to monitor a patient's compliance and it's a very difficult task interpreting urine drug testing because it involves understanding the metabolism of drugs. And I would make reference here to Reisfeld's article appearing in the Annals of Clinical & Lab Sciences, 2007, which has a very excellent review of how to properly and effectively determine drug monitoring.

On Slide 37, I did a screenshot here for you of the Agency Medical Directors Group, which is a Washington State alliance of State agencies using a - and I would say a very strong support from clinical providers; in other words, not academicians, but people actually take care of patients as well as academic resources. In fact, when I first joined this group, I was working as a clinician in a private practice setting. I had been involved in the development of this project, and our latest 2010 update is available and the online link is up on the right of the screen, www.agencymedicaldirectors.wa.gov. It's available as a PDF to take a look at.

Another alternative is a tool that is now proprietary and on 38, Slide 38, you can see, again, a screenshot of this process in development. We here at the University of Washington are collaborating with CPAIN and you can get on to their site as I've listed below.

And our hope is as an internist I would say to be able to get a quick snapshot of how I'm doing with my patients. It's just like I might monitor electrolytes when I put a patient on a diuretic or their renal function or monitoring a CBC in response to treatment of anemia, I'd like to see, for instance, that the pain intensity in the past week has declined.

And, as you could see, this gives us a follow-up, an initial intake and then in this individual case of December 2009 through June 2010, highest, average, lowest pain relief in the past week, and you can read yourself the other domains that are use - involve the six classic domains in terms of pain interference with quality of life, disability, functional goals being met, and the IPAQ functional assessment of activity.

This process and the CPAIN tool is being further developed. One can produce any of these on an ad lib basis to monitor patient outcome, but, again, the key point here is that we need to be monitoring patients if we're putting them on opiates to assess whether we're doing them any good at all.

The very simplest tool, this also comes out of the Agency Medical Directors Group, one can be, on Slide 39, just two simple questions. What is the pain intensity? And how much does that interfere? And if this were offered at sequential visits, the docuability to document a favorable opiate response would be - is obviously self-evident.

On Slide 40, there's a summary, this also appears in the AMDG guideline that I alluded to before, the variety of public domain screening tools that require no cost to obtain and links are available. And at the top there you can see the Opioid Risk Tool, the PHQ-9 as you move further down, and the other

addiction monitoring tools that, again, should be offered on a continuing basis, certainly for patients at high risk.

One Slide 41, you can see, for instance, the PHQ-9, which I actually downloaded off that site to assure that it was working. And this - and we've timed it in the office that it takes about 15 seconds for the patient to run through this sheet and you can give a quick positive score and the site actually gives you evidence-based data to indicate significant depression that may need to be managed. And, as a practitioner, if your patient's having a deteriorating PHQ-9 that indicates that you're not doing well with your patient.

On Slide 42, it's just for a quick look, the Roland-Morris Questionnaire that I spoke about before. This was originally developed for back pain, but this version has been modified for any possible pain condition. And you can see there's 24 questions and it's a positive or negative and you can score your patient that they're a 24, a 24 positive, which would indicate a, you know, profound disability, and that as one continues one's opiate prescription on an ongoing basis, one would expect a valid response to show an improvement in functional capacity.

Slide 43 shows the Opioid Risk Tool. Again, you can see how simple and straightforward it is. And I think also interesting to see per Dr. Paulozzi's remarks, for instance, Item 3, for age 16 to 45, the high risk groups, just being that age group raises your opiate risk. And other important questions that are identified in terms of psychological comorbid active diseases that may be present.

Again, the importance of balancing, as I show on Slide 44, the risks and benefits, and so then the challenge as providers then is we achieve our goal at least is to develop a satisfactory analgesic program where pain is reduced, the quality of life is improved, and that functional capacity is increased.

And on the other side managing the side effects, the drug/drug interactions these opioids may have, and as we learned just a few moments ago how catastrophic the accidental overdose issues are. And I would clarify in Washington State the current incidence of death by accidental drug overdose now exceeds the death rate by car accident, so we're taking a lead in the wrong way.

And I list also the risk of opioid induced hyperalgesia, here on the bottom, only because that's a significant concern that practitioners will often raise, and I'll speak to that in a minute.

The clinical opioid pharmacology on Slide 45 is listed there for completion because we do talk about pharmacology and we do know that opioids work in a variety of signal modulation effects. The important distinction here is that they are an analgesic, not an anesthetic, so if the patient is expecting to have no pain at a site in their body where they're taking an opiate to manage, they will perceive only a reduction in the pain intensity and that the perception of pain is narcotized rather than actually blocked. To get a true anesthetic effect, one needs to do a regional anesthetic procedure.

So if the patient's expectations and, more importantly, the provider's expectations are that we're going to get complete pain control, we will fail and fall into the default raise the prescription dose when the patient comes in

saying they're not getting relief rather than identifying the fact that we're at about 30% improvement, that's about all we're going to get and we need to move on to another treatment domain.

Again, one of the big problems, and we know, for instance, for overdoses on methadone that the most common timeframe for overdose on methadone is early during the dose initiation phase, there's a variety of studies available to confirm that, and certainly we have experienced anecdotes where patients are put on as a naïve individual to opioids, a long-acting product and have an adverse outcome.

So as an absolute rule, for acute pain, short-acting agents are the drug of choice and not long-acting agents and for chronic pain we want to use the lowest MED, the morphine equivalent dose, possible and whatever that dose might be in a combination of long and short-acting agents as necessary, certainly patients who are having breakthrough pain between doses of a long-acting agent would be a standard and typical approach.

So on Slide 46 I've summarized what an opioid trial should be. It isn't very complicated. I think as an internist or any primary care practitioner who is listening in here would be the - just the way we would assess response to a blood pressure treatment or a response to diabetic treatment. We want to see if the patient is going to respond to the drug that we offer.

So the term I think useful is, is this an opiate responsive pain. We use four domains to assess. Is there analgesic effect? Is there activity improvement? Is there an adverse effect of the drug, a direct side effect? You know, typically we would expect some degree of constipation, but if there's cognitive

impairment, driving impairments or other adverse effects that are more significant, that would need to be noted in your ongoing record. And then, of course, is there any aberrant behavior? Aberrant behavior again referring to the misuse or abuse issues that were discussed earlier.

And the other principle of an opiate trial is that we have an intention to discontinue the opiate if a patient is not improving or at least reduce the dose when the risks begin to exceed those benefits.

The term opioid rotation I apply here in this slide only to demystify that term. The switching from one opioid to another to assess for opioid responsiveness is far less certain an effective approach to management; and if a patient's been on an opiate for a long period of time, there's very little evidence that, well, it's time to switch to another opiate to reduce tolerance or dependency. That's often associated with a complicated dose equivalent conversion and a very disrupted regime. So my general practice is when a side effect occurs and we still feel that there is an opiate responsive situation going on that a switch to an alternative opioid - a somewhat equivalent - working equivalent dose would be appropriate.

Slide 47 is my cartoon version of what opioid induced hyperalgesia is all about. We can see on the increasing dose axis, the X axis, that as we increase the dose, the orange color, the analgesia, we expect it to rise, but at some point we hit that 30 to 60% improvement response and we're not going to see a patient get better. And we're observing now, certainly in animal studies and in a limited number of human observation studies, that the effectiveness of opioids begin to drop and that term refers to opioid hyperalgesia.

It's unclear what that dose is; but certainly as the increasing dose rises, we cross the threshold where adverse effects, on the far right, begin to exceed analgesic benefits; and we call it the therapeutic window that we try to strike where our adverse effects, our risks, are not greater than our benefits. And on the left, you can see that the incre- the opioid induced hyperalgesia is actually a rise of analgesia and then a decline as the patient dose increases.

You know, in line with this, on Slide 48, the American Board of Pain Medicine, it's in - published in Pain Medicine 2009, it has a very succinct and, I believe, an accurate way to approach the management of patients - of opiates. In other words, it's to avoid primary reliance on opiates and when they are used alone or in a non-coordinated fashion, it leads to poor outcomes. And, as they say, when employed as a sole treatment, it's associated with significant societal expense and treatment failure.

One Slide 49, the Agency Medical Directors Group has a - I view it, a nice conversation that is worth having with yourself as well as your colleagues about what to do as you start rising in your morphine equivalent doses. And as supported by the recent publication annals this year from the Seattle group, we ran up the number of 90 to 120, and this was based on clinicians' judgments about where we start seeing problems with opiates, and now we have some nice confirmatory science to support that, at about 100 your patients are going to start to run into trouble.

So the AMDG guidelines basically say at 90 milligrams take a deep breath and decide if you're doing the right thing, be certain all your I's are dotted and T's crossed about the four A's, the analgesia, the adverse effects, the aberrant behaviors, and improved activity. And certainly above 120 milligrams it's

really time to basically take five breaths and just determine if indeed higher doses are going to lead to improved clinical outcomes.

All right. So how do we convert opiates? It's quite straightforward. On Slide 50 I've listed here for your reference morphine equivalences morphine at 30 milligrams, this is oral, this is not parenteral. At parenteral you - it's two to three times conversion into IV, so that's down on the bottom left reference. But you can see that, you know, morphine is - that's our standard converter, we would want to convert everything into morphine equivalents.

A comment on methadone, on the right, it's a hazardous drug because it has a - basically a logarithmic increase in potency due to its complex pharmaco-dynamics. At less than 30 milligrams it converts as about three to four and you can see at the bottom at greater than 60 milligrams, you - we're doing a multiplier of 12.

So on Slide 51, I've went to the AMDG site to the opioid dose calculator, which you can download and I recommend you put on your handheld device or on your office computer. You can click right on that tool and have it ready and accessible. And here I've put in morphine - excuse me, methadone at 80 milligrams. I've just added that and you can see that converts out to the shocking MED of 960, which years ago would not have been a dose of methadone that many of us would have thought to be too hazardous, but at this point judging from the newer data, we can see that this is a very problematic and quite high dose.

And on Slide 52, here I give you some caveats on methadone that it has a very significant dose accumulation. It had some advantages perhaps for

neuropathic pain as an NMDA antagonist. It also works a little bit on where we treat tricyclics in terms of hydrox - or serotonin and norepinephrine reuptake, but a significant QT prolongation, which is dose dependent, and a significant urine elimination like morphine that needs to be dose adjusted in renal failure. It has significant cytochrome activity. And, for your reference, I won't go through that, but you can see there's inducers and inhibitors that will affect many other drugs on the patients on methadone.

So an opioid trial, on 53, very straightforward and I summarize this and I won't walk through all of the points for the sake of time, but start with the short-acting drug. If necessary and appropriate convert to long-acting equivalents. Keep your dose between 90 and 120. A strong admonition to avoid benzodiazepines and other sedating drugs due to the complex toxicities. Do the four A's, which I've listed in Step 5, regularly and in every visit. And then if a patient is not responding, one could do a dose reduction of 10% every one to two weeks.

And if the patient has a urine drug toxicology positive for methamphetamine or cocaine, we here at the University of Washington, and I would endorse that this be done anywhere, that is clear evidence of diversion and high risk and is grounds for a summary dismission - dismissal from our clinic.

On Slide 54, we recommend here at the University of Washington that at about 90 days we inform our patients that if they're on opiates for that long, they're probably going to be on them for the rest of their life, and that this represents a continuous side effect management issue. The listed issues include both driving and hypogonadism, that's sleep abstinence, et cetera, and

offer a urine drug test at that point and an informed consent agreement as well.

On Slide 55, again, reiterating what Dr. Paulozzi mentioned that abuse is aberrant behavior or misuse. The same categories that he's described. And often terminology is that if my patient is a Vicodin addict, using a brand name there, because they have physical dependence that does not describe abuse or addiction that just describes a physiological state of regular use and is not a term that would indicate abuse or addiction.

Monitoring toxicology, on Slide 56, is complex because point of service is - needs to include oxycodone, methadone, benzodiazepines, and many of the products don't include these, that typically confirmation testing is required at significant cost. And remember determine metabolism where the reference I've offered earlier that codeine ultimately becomes hydromorphone or as this hydrocodone becoming hydromorphone and so that these do not represent aberrant results. So the interpretation is critically important.

Slide 54, again, discusses very briefly the - excuse me, the - I'm sorry, Slide 56, the toxicology management. And Slide 57 is the model that primary care doctors often can use to determine when a pain specialist may be helpful to provide advice. And the algorithm would be as we would do with a cardiology concern, chest pain that is suspicious for heart disease we refer for a cardiologist for specific interventional assessments and outcomes and then referral to a surgeon or specialist if indicated.

If your patient is not doing well in terms of pain management, it would be like sending your patient to a cardiologist when they are in Class IV New York

Heart Association failure rather than when they have the first sign of problems. So the goal would be to get help early and often.

So best practice on 58 is listed; start with a non-opioid except in acute injuries when appropriate; avoid concurrent sedatives; follow those four A's; induce - introduce rather an agreement and urine drug testing at 90 days; keep your dose below 100 to 120; and, again, as I said a moment ago, get help early and whenever it's not going according to expectations.

And I thank you for your attention. I know I've covered a lot of material and though I'm living on the West Coast, I am from New York so I speak awfully fast. And so hopefully there will be time for questions. Thank you.

Loretta Jackson-Brown: Thank you, Dr. Paulozzi and Dr. Tauben for providing our COCA audience with such a wealth of information. We will now open up the line for the question and answer session.

Coordinator: Thank you. If you would like to ask a question, please press star 1, please record your name so I may introduce you. To withdraw, press star 2. Again, to ask a question, please press star 1. It will be just a moment for our first question.

I do have a question from (Caroline Tudor). Your line is open.

(Caroline Tudor): Yes, hello.

Dr. Len Paulozzi: Hello.

(Caroline Tudor): Yes, I'm a chronic pain patient. I had several back surgeries and neck surgeries. I've been on and off opioids for 15 years. I currently am off them. I really don't want to go on them. I - it's kind of a spiritual issue. However, they do give me a quality of life. I can't function without them. I'm 54 years old and I - is it safe for me to go on them the rest of my life? I mean, I'm concerned about dosing up and how often you do that and I just don't know what's the best thing for me to do.

My doctor, my therapist, my parents, my family, they all say get out of bed, get on morphine, it's unkind to be in pain. You know, you can move and have a quality of life and function when I'm on it and I can't when I'm not. Do you have any recommendations?

Dr. David Tauben: Well, let me take this first as the clinician. First, we're not prepared really to provide clinical care recommendations in this context.

It's very important that you have established a relationship with a consistent single primary care provider, that your primary care provider is aware of your concerns and of the observations of your family that you show improvement, that the primary care provider be familiar with the concerns about the dose escalation and the objective to keep the morphine equivalent dose as low as possible, and the concerns about the addition of sedative-hypnotic drugs, which can lead to significant adverse effects, and the very important role of the other non-opioid modalities that are very helpful, such as cognitive behavioral therapy, you indicated you had a therapist, but doing relaxation, getting regular and consistent physical exercise on a scheduled structure basis...

(Caroline Tudor): So...

Dr. David Tauben: ...and collaborating with the rest of your care team.

(Caroline Tudor): Okay. And I do have a primary care physician who also thinks I should be on it. Should - is that good enough or should I go to a pain management specialist to - you know what I'm...

Dr. David Tauben: I think that's worthy of a conversation with your primary care doctor. I think you should sit and say I'm worried about my being on opioids. I've got lots of mixed feelings, I have spiritual concerns, I have family concerns, you know, let's have a conversation.

Most primary care doctors don't like to talk about pain because we're not typically trained much in this and so you'll probably need to bring up the conversation. And if the primary care provider says let's get help or if you indicated I'd like a second opinion that would be a very good launching point to take this to the next step.

(Caroline Tudor): Okay, well, this has been extremely informative, especially dosage wise, and I just thank you so much for this opportunity to...

Dr. David Tauben: You're very welcome.

(Caroline Tudor): Okay, thank you.

Coordinator: Thank you. Next we have (Tina Ermine). Your line is open.

(Tina Ermine): Yes, good afternoon. I'm wondering if you have any thoughts on the role or the impact of the FDA REMS program on the long-acting opioids. I'm a substance abuse counselor in Northern Virginia and I've been following this very carefully. But I wonder if you have any thoughts as far as prescribing practices and how this will impact the medical professionals.

Dr. David Tauben: Len, can you handle this one. I think this is up your alley more than mine.

Dr. Len Paulozzi: Sure. This is Len Paulozzi. As you know, there was a recent FDA hearing with an advisory committee to discuss the REMS and the FDA recommendations for the REMS were not - or a description of the REMS they're proposing was not accepted by the committee. So it remains unclear what shape, what form the Risk Evaluation and Mitigation Strategy will take as we move forward here. So...

(Tina Ermine): Do you think it will be a good thing if it does move forward in some shape?

Dr. Len Paulozzi: Well, I think the - mitigating the risk is a good idea. The difficulty is picking the most effective national strategies for addressing that.

(Tina Ermine): Okay. Thank you so much.

Dr. Len Paulozzi: Sure.

Coordinator: Thank you. Next we have (Robert Kirkpatrick). Your line is open.

(Robert Kirkpatrick): Good afternoon. A quick question for you. In our state, in Tennessee, hydrocodone is very far up the list in number of prescriptions, but much

further down the list in the cost of those prescriptions. Providers are concerned, insurance companies are concerned about the non-opioid prescribed - prescriptive drugs that are very expensive, but not so addictive, if you like that term. Any comment from either of you about the choices and the financial or social impact of it?

Dr. David Tauben: I can - this is David Tauben, let me get right in on the clinical side. We - just as a point of fact, the United States consumes, I think, over 95% of the hydrocodone manufactured on the planet Earth, so we do use a lot of hydrocodone. It's a very effective analgesic, but, again, it's short-acting and patients will get three to four or maybe five hours' worth of relief when they take that medication.

So the use of a short-acting drug over a long period of time typically runs into problems for the patient. They wake up at night in withdrawal, they will take extra doses during periods of heightened pain in a setting of increased tolerance, so long-term hydrocodone use on a scheduled basis is generally not recommended.

And I understand the costs are low. There are generic versions of long-acting morphine products now available, which are often cost competitive. And I would also add methadone to your prescribing familiarity. And knowing the logarithmic increase and all of the drug/drug interactions, it's still one of the best pain drugs we've got and is exceedingly cheap. I think it will be even be cheaper than the hydrocodone.

Again, you would do the MED conversion of your hydrocodone, which would represent one to one on morphine. You run it through any kind of converter

you'd like, dose it down by 60, take only 60% or less for safety's sake. Anticipate that will take three days before drug levels in the patient's body are matched because of the long half-life of the drug and go at it, go slow, and slowly transition the patient perhaps over to methadone entirely.

And occasionally we'll use rescue drugs and that would be associated with specific functional activity requirements, such as going to the gym, such as playing with one's children at the end of the day a game of catch, such as doing particular household chores. So the PRN use of any short-acting drug should be tied to a specific functional activity that can be supported and then the long-term agent would be useful for managing the clinic - you know, the chronic continuing level of analgesic that's necessary.

Dr. David Tauben: I look to Dr. Paulozzi, if there's any comments about hydrocodone from the - your perspective.

Dr. Len Paulozzi: No, it's indeed the most prescribed drug in the United States. And I think the issue really here as always is cost of drugs and we sometimes make decisions based on cost. I think cost is one factor then the other thing, of course, is to look at the risk profile and how the drug is being used by individual patients. Cost comes into choices for Medicaid formularies, for example, and health plan choices with the preferred drugs. I think the - I guess my point is that it shouldn't all be driven just by cost because we can potentially make the wrong choice for a patient if cost is the only consideration.

(Robert Kirkpatrick): That was my main question had to do with Gabapentin or topical Lidocaine, those kind of things that are extraordinarily expensive compared to

the generic opioids. How do you handle that discussion with your patients or with your providers or with your insurers?

Dr. David Tauben: Let me jump in there right away on the indications for using an antiepileptic such as Gabapentin and in my view would require a diagnosis of a neuropathic pain condition rather than a - one that we would consider a direct, you know, a tissue trauma type injury from a nociceptive perspective. You know, and Gabapentin's efficacy is limited. If we, again, used a 30% rule, we're going to get about 30% relief with Gabapentin.

The studies in fibromyalgia, which is probably some of the better ones, or peripheral diabetic neuropathy, show success at about 30% reduction in pain, at the higher doses maybe 50% at best. So we're not going to get that much mileage out of Gabapentin and hence it's a total waste of money if you're using it for the wrong indication; in other words, a nociceptive pain problem like a, you know, chronic arthritis difficulty as opposed to a nerve-based pain syndrome for which at least there's some evidence-based data.

(Robert Kirkpatrick): Thank you.

Dr. David Tauben: Thank you.

Coordinator: Thank you. Next we have (Charles Thomas). Your line is open.

(Charles Thomas): Hello. I may have missed it, but I didn't hear much mentioned about a tool of the Prescription Drug Monitoring Programs that are available in, well, 40 plus states now, I think, at least. And I think it's a great tool for practitioners and pharm-dispensers to look and query their patients; and it's available in quite a

few states now. And you find out that a lot of patients that you never suspect are actually getting prescriptions filled and prescribed in a number of different places. Any comment on that?

Dr. Len Paulozzi: Yes. This is Len Paulozzi. I appreciate your brining that point up, Charles. Prescription Drug Monitoring Programs are in operation in 35 plus states and have been passed into law in 43 states and one territory as of this year. So - and many of them are rapidly improving their ease of access turnaround time for reports to healthcare providers about individual patients.

I agree that it's extremely important to make use of this tool before starting somebody on chronic opioids and periodically during the course of care to see whether the patient is getting the same or similar drugs and other scheduled drugs from other healthcare providers.

Simply asking patients questions about whether they are using or misusing drugs has proven in a number of studies to have really been inadequate. And telling patients that you are going to be checking their records in Prescription Drug Monitoring Programs I think is a reasonable part of the initial discussion to have with individual patients.

Dr. David Tauben: I would actually second that very strongly as well and it was an excellent comment, Charles. Washington State actually doesn't have the funds-- it’s a law, but we ran out of money with the current economic crisis to put it into effect. So we're one of the laggards as far as actually putting one up and running.

The problem, as best I understand it, with the PMPs is getting the data to the provider in a timely, almost real-time fashion; so I would urge that any state that does have an active PMP or is planning one take - and physicians in that state or providers in that state who have ability to contact their legislative representatives and the governing boards encourage that the PMP be a real-time access to the provider, not just be locked up in some storage cabinet where we don't know what's happening or become primarily a tool for law enforcement. Many states are really directed towards law enforcement activity and the provider can't even get access to these very critical data.

So if a PMP is available, it needs to be used by providers absolutely and we have to get access to it. So as these evolve into better and better tools, we need to play an active role as prescribers in having something that's useful. So thanks for bringing that up and contact your legislation to make sure you go ahead and get that on a regular basis if you're in a state that does have a functioning PMP.

Loretta Jackson-Brown: We have time for one more question.

Coordinator: Thank you. (Denise Trainer), your line is open.

(Denise Trainer): Thank you. Hello. I work primarily with seniors and I'm interested in their low risk of misuse and overdosing given that gender, chronic pain issues, and mental health issues would still come into play. So can you speak to what protective mechanisms might be at play there and is there anything to be learned from that?

Dr. Len Paulozzi: Well, from the epidemiologic perspective, you're correct. We just see lower rates of overdoses and non-medical use in emergency departments for people over the age of 65 and lower self-reported rates of non-medical use of the drugs. I think this is in spite of the fact that most studies which say that people over age 65 probably are prescribed as much or more long-acting opioids than people in middle-age in - even though most of the overdoses are in people in middle-age or people in their 20s.

I think what it reflects, in part, is a reduction in substance abuse, a tendency for substance abuse among the elderly. Some of this may just be a normal effect of aging; some of it may be, you know, a cohort effect of the generation that people were born in affects their behaviors. There is concern that baby boomers, people now in their 40s and 50s, are unusually receptive, if you will, to drugs and the abuse of drugs and we may be seeing rates rising among people over 65 as the baby boomers reach retirement age.

So I think it's a good point because many people are concerned that the problem is mistakes being made with polypharmacy, lots of drugs to manage by providers, or patients who are older getting confused about the number of medications and the dosage and the timing of their drugs. This does happen and probably we need to guard against that. But, by and large, the difference is the lack of a deliberate nonmedical use of the drugs in people in this age group.

Dr. David Tauben: Yes, and let me just add a few other thoughts in our closing minutes here. Generally, we know in the older population they take fewer of their meds than we even prescribe. Some of that is for financial reasons, others are based on, as talked about, my - just mentioned a few minutes ago, the cohort is a little

less willing to get medicalized and take drugs for every possible condition. So the concerns about the aging boomers have - is very valid and I think we have to pay careful attention to the attitudes of the group we're managing.

One other comment that, (Denise), your question brings up is the issues of diversion because many of these patients do receive opioid prescriptions for a cancer-based diagnosis or other chronic pain conditions.

(Denise Trainer): Right.

Dr. David Tauben: And that many of the teens that we saw the data earlier presented are presenting at emergency departments or dying, and to state, again, they're competing with car accidents in that age group, most of the drugs are obtained from their family members' medicine cabinets.

And it's a very important area that practitioners need to be being attentive to is that these drugs be locked up, secured, and if a patient is not taking the opioid, you know, if they say, for instance, oh, doc, you gave me, you know, 100 last month and I hardly use it, and you've the tendency, well, let's take 100 so you don't run out, it's not indeed not what should be done because they'll probably fill it and then their grandchild or friend of the grandchild may come to the house and they can take that bottle and sell it or use it and in a very dangerous fashion.

So as we saw that the rise in deaths increases with the rise in available prescribed drugs, we want to be certain to keep our prescription amounts down low. So if it's a ten oxycodone event, give ten, not 50. Let's have the patient come back. If the patient's on chronic meds and not using them

regularly, as many of the older patients do, have that conversation and stress the importance of diversion for their family.

Partnership For a Drug Free America has a wonderful set of posters. One of them shows a young girl saying that I got my eyes from my mom and my mouth from my father and my drugs from my grandma's medicine cabinet, and that's a big campaign that we also need to get out there. And the people to educate for that are that older population that are getting the drugs and not taking them.

(Denise Trainer): Thank you.

Dr. David Tauben: Thank you.

Loretta Jackson-Brown: On behalf of COCA, I would like to thank everyone for joining us today with a special thank you to our presenters, Dr. Paulozzi and Dr. Tauben. If you have additional questions for today's presenters, please email us at coca@cdc.gov, put Dr. Paulozzi and Dr. Tauben in the subject line of your email, and we will ensure that your email is forwarded to the presenters for a response. Again, that email address is coca@cdc.gov.

The recording of this call and the transcript will be posted to the COCA Web site at emergency.cdc.gov/coca within the next few days.

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A link to the June 18, 2010, MMWR on "Emergency Department Visits Involving Non-Medical Use of Selected Prescription Drugs in the United States 2004 through 2008," along with additional resource links, can be found on our COCA call Web page under the announcement for this call. That Web page, again, is emergency.cdc.gov/coca.

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Thank you again for being a part of today's COCA conference call. Have a great day.

Coordinator: Thank you. That concludes today's conference. You may disconnect at this time.

END