Methadone for Pain Management: The Clinician's Role in Reducing the Risk for Overdose

Moderator: Loretta Jackson Brown

Presenters: Len Paulozzi, MD, MPH and Dr. David Tauben, MD

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Operator:

Welcome and thank you for standing by. All participants will be on listen only until the question and answer session. Today's conference is being recorded. If you have any objections you may disconnect at this time. I'd now like to turn the meeting over to Loretta Jackson Brown. Thank you. You may begin.

Loretta Jackson Brown:

Thank you, (Melinda). Good afternoon. I'm Loretta Jackson Brown and I'm 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 Webinar, Methadone for Pain Management: The Clinician's Role in Reducing the Risk for Overdose. We are pleased to have with us today Dr. Len Paulozzi from the Centers for Disease Control and Prevention and Dr. David Tauben from the University of Washington's School of Medicine, here with us today to review the epidemiology of methadone overdoses in the United States and discuss guidelines for appropriate opioid prescribing.

You may participate in today's presentation by audio only, via Webinar, or you may download the slides if you are unable to access the Webinar. The Power Point slide set in the Webinar link can be found on our COCA Web page at emergency.cdc.gov/coca. Click on Coca calls, the Webinar link and slide set can be found under the call-in number and call pass code.

At the conclusion of today's session, the participant will be able to discuss the role of methadone in fatal drug overdoses in the U.S., compare and contrast methadone prescribing to other opioid analgesics, and state circumstances under which use of methadone might be appropriate.

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Our first presenter is Dr. Len Paulozzi. He's a Medical (Epidemiology) in the Division of Unintentional Injury Prevention in CDC's National Center for Injury Prevention and Control. His area of concentration is drug overdoses, especially those due to prescription drugs. He has been concentrating on the drug overdose problem since 2005. Dr. Paulozzi has authored and co-authored more than 80 publications during his 28 years in public health. He has testified at Senate and House briefings related to prescription drug use and his work is frequently cited in both the popular press and scientific literature.

Our second presenter is Dr. David Tauben. He has 30 years of internal medicine, community, primary, and consulting care experience in Seattle, Washington. He joined the University of Washington's faculty as a full time clinician and educator in 2009. He is Board Certified in both internal medicine and pain medicine. He is the Director of Medical Student Education in Pain Medicine at the UW, jointly appointed in the Department of Medicine and Anesthesia and Pain Medicine. A faculty member at the University of Washington's Center for Pain Relief, his group was 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 tele-medicine project across Washington State, Wyoming, Alaska, Montana, and Idaho.

Again, the Power Point slide set and Webinar link are available from our COCA Web page at emergency.cdc.gov/coca. At this time, please welcome our first presenter, Dr. Paulozzi.

Len Paulozzi:
Thank you. And welcome to this COCA seminar. The material I'm going to talk about today is largely derived from an MMWR article that was published recently, actually on July 6, 2012. And you can see some of the references that I'm talking about cited there. I have some additional information here that is not presented in that MMWR article. Just by way of background, I'd like to describe the drug poisoning problem for you in the United States.

This figure shows rates per 100,000 for leading causes of injury death in the United States, motor vehicle traffic, the white line has come down in recent years. And in 2008, drug poisoning and poisoning in general passed motor vehicle traffic mortality. In 2009, drug poisoning shown in orange on this figure exceeded the number of deaths for motor vehicle traffic in the United States for the first time in U.S. history. If you look at the more recent trends in drug poisoning and break them down by specific type of major drug type involved, you get the results shown in this figure. Between 1999 and 2009, what has happened has been a dramatic increase in overdose deaths involving opioid analgesics or opioid pain relievers. Cocaine shown in white, mortality peaked in 2006 and is coming down. Heroin mortality has remained below the other two categories.

A few years ago, the number of deaths involving opioid analgesics in total exceeded the sum of deaths involving cocaine or heroin. As of 2009, there were approximately 15,500 overdose deaths of all intents, that is included unintentional suicides and so on that involved opioid analgesics. And if you break down the trend line for opioid analgesics into component parts, you can see the following categories shown now on Slide number 9. The top line is a category of opioids derived from opium that are semi-synthetic, hydrocodone, oxycodone, morphine, and codeine. The green line is methadone. The bottom line is synthetic opioid analgesics such as fentanyl and meperidine. And what's happened during this time period has been an increase in all three categories. But methadone mortality rose faster than the other categories. It peaked in about 2007 with roughly 5000 deaths involving methadone in the causation.The other categories have gone up since that time. Methadone mortality rates are still just about 5000 as of 2009.

Next Slide, number 10, in this slide I take the methadone mortality rates, methadone related overdose deaths shown in the red dotted line in the middle, and compare it with methadone use for pain in the United States as measured in kilograms per 100,000 people. And this data comes from the Drug Enforcement Administration. It does not include methadone used in opioid treatment programs.

The bottom dotted line is the rate of methadone prescribing for pain per 100 persons in the United States. So as you saw earlier, the mortality rated peaked in 2007. Paralleling that, the use of methadone for pain also peaked in 2007. However, the prescribing rate stayed relatively stable after 2007. So what's happening is that there are fewer milligrams of methadone per methadone prescription after 2007. This may be a result of black box or boxed warning that FDA applied to methadone late in 2006 and/or DEA's restriction on the use of the 40 milligram formulation on methadone to opioid treatment programs and hospitals. So it was no longer available for prescribing in the outpatient setting for pain.

Slide number 11, we can only learn a limited amount from death certificate data so we have to supplement that with studies done in individual states that have state medical examiner system. A number of individuals have studied this problem over the past 10 years and six studies are shown on Slide number 11. Basically, what it indicates is that, in the second to last column, there's 25% or fewer of people who die of methadone overdoses had been enrolled, or were enrolled in their state opioid treatment programs at the time of their death. And we also know, in fact, that most of the overdose deaths, in where it has been studied, involved the pill form of methadone rather than methadone liquid. So this leads to the conclusion on the part of everyone who's looked at this issue that these methadone overdoses are primarily from methadone being used for pain. The last column shows the percent of people who had a prescription for methadone, in something like the state prescription drug monitoring program. And as you can see, a minority in all the study had prescriptions, indicating that a lot of methadone is being diverted from being used for pain and is being used without a prescription by people who ultimately overdose on it.

Slide 12, this is data from just 13 states rather than from the whole country. It is from 2009 and it comes courtesy of the Substance Abuse and Mental Health Services Administration's Drug Abuse Warning Network Medical Examiner component, otherwise known as DAWN. And it shows for these 13 states on this slide, the numbers of deaths that are related to the major types of opioid analgesics. And this is a kind of breakdown that you can't do with death certificate data.In the figure on the left you can see that methadone, shown in the hatched pattern, the number of methadone deaths in these states in this one year was comparable to number from oxycodone. If you look at the right figure, the bars in red indicate however, that when you're looking at deaths that only involved a single drug of any kind, methadone stood out from the other opioid analgesics with 298 deaths in these states in this one year where methadone was the only drug involved.

If you take the same data, same source, and convert it to rates, the pattern is revealing. These are rates calculated by using kilograms of morphine equivalents of opioid analgesics as the denominator. So in the left figure, for all drug related deaths, you see the rate of death for every ten kilograms MME. In this figure, as in the previous figure, methadone is shown in the hatched line, and its rate exceeded that of any of the other opioid analgesics. And not unexpectedly, in the figure on the right for single drug deaths, the rate for methadone was greater than any other opioids. These differences were all statistically significant. These differences will also continue to be statistically significant even if one subtracted 25% of the methadone deaths to allow for some of the deaths potentially being related to methadone use in opioid treatment programs. So there's a large difference there between methadone and other opioid analgesics.

Slide 13, this is data that comes from SDI Vector One, a national survey of prescribers, the analysis originally done by Laura Governale of the FDA and presented in 2010. It shows the distribution or percent the methadone prescriptions for pain by prescriber specialty. Forty-three percent of these prescriptions were made by primary care physicians, 9% by mid-level practitioners and the others by a variety of specialties. So the majority of the prescriptions as of 2009 were being written in the primary care setting. And in the same survey, same analysis, you can examine the percent of diagnosis that were associated, different types of diagnosis associated with methadone use, in this office-based physician survey. Forty-six percent of the prescriptions were associated with muscular-skeletal disease problems, in particular back pain, 17% were associated with headaches, 11% with cancer, 5% was trauma, 4% was a category known only as general symptoms, 4% for drug abuse and dependence, and 13% for all others. When you look at the distribution of methadone for pain by state, using the DEA data, there are wide variations across the country.

This map on Slide 16 shows the percentage of opioids that were accounted for by methadone. The darker the color, the darker blue, the higher the percentage. And the darkest blue ranges from 11.5% to 18.5% of the Morphine Milligram Equivalent that were distributed in that state, in the United States in 2010. So there's a several fold difference from states using little methadone and states using a substantial amount. Potentially related to this is the map shown in Slide 17 which indicates that methadone is the preferred long-acting opioid analgesics on the Medicaid formulary of some 31 states in the United States. And this data comes from 2012 so it was just ascertained within the last couple of months, again wide-spread use of methadone as a preferred long acting opioid analgesic by Medicaid programs.

Slide 18 turns to what can we do about preventing this problem? For states, they can develop and promote the use of safe prescribing guidelines for methadone. They can support their prescription drug

monitoring programs and staff there, to identify patients who are using methadone or other prescription pain killers for non-medical purposes. And obviously a lot of drug is being diverted to the individuals who died of overdoses. And of course they can continue to support the use of methadone as a treatment for opioid dependence in opioid treatment programs.

Slide 19, health insurers have an important role to play. They can evaluate methadone's place on preferred drug lists. This can be both private and public insurers, such as Medicaid programs. They can consider strategies to insure that pain treatment with any dose higher than 30 milligrams of methadone a day, that's the recommended maximum daily starting dose from the FDA, consider strategies to insure that any dose higher than that is appropriate. And health care providers, last but not least, health care providers need to follow guidelines for prescribing methadone and other prescription painkillers correctly. They can choose not to prescribe methadone if they don't have training and experience with its use.

Methadone is really not a drug for amateurs. And they can educate patients on how to safely use, store and dispose of methadone. Thank you for your attention. I'm going to pass the microphone to Dr. David Tauben.

David Tauben:
Thank you, Len. That was informative and leaves us with my first slide, which is Slide 22. What's a prescriber to do with this kind of data? It sounds pretty terrifying, particularly for the primary care folks who do not have the experience and advanced training necessary. So my hope is, in the next 20 minutes or so, to give a very quick run through of some general principles and as my early introduction described, I am involved in academic work in the University Washington in the division of pain medicine. I am, by original training a primary care provider and spent 27 years in the trenches working with this problem of chronic pain and recognizing that there is indeed a value for methadone. So my objective - by the way, no disclosures of any interests and I'm happy to state that we are a part of the National Institutes of Health Pain Consortium Center Excellence and Pain Education. And we thank NIH for that support.

So the objectives are going to be, as implied by Dr. Paulozzi, that well my understanding, the indications for the use of methadone, be knowledgeable about its risks, follow safe methadone dosing practice and know why and how to apply the guidelines for opioid management and monitoring, particularly in the setting of methadone which we see does present unique hazards and as well stated is not for amateurs.

On the other hand, this is not intended to discourage primary care prescribers of all specialties to becoming a bit, become a bit more expert so that they can indeed use this very helpful drug.

So my Slide 25, for those following on PDFs, is a brief description of the basic clinical pharmacology. It's an excellent pain drug because it is a potent Mu-agonist, meaning it binds directly to the Mu-opioid receptor and has potent analgesic effects. Its challenge, however, is involved in the variability of absorption, which you can see is broad, oral a very wide range, 3-fold range of expected absorption orally. And the peak plasma levels are also up to a 2-fold range. And even more importantly there is up to a 30-fold inter-patient variability in both steady-state concentrations and in expected peak concentrations. We also can expect that age and illness of our patient increases toxicities, and I'll spend some time with those particular subsets in a few moments. That there are frequent drug-to-drug interactions which add to the complexity of prescribing this pharmacologically complex drug, that the drug is metabolized 100% through the liver and its phetachrome metabolic pathways and there being no active hepatic metabolites, it is very important to be able to use methadone properly in patients with liver disease. And it may give us a bit of a free pass, a bit, on our patients who may have renal disease as there's no active metabolites, and we're just discussing basically first-pass clearance of the effect of methadone in patients with renal insufficiency.

Some special features that make methadone a particularly helpful drug and also a bit more challenging to prescribe are listed here on Slide 26. It is an NMDA antagonist which has unique properties in that it is thought to play a role in its potential for reducing the development of tolerance for opioids. It also has some non-opioid analgesic effects working on the NMDA receptor. It also, interestingly, has some 5-HT and norepinephrine reuptake in addition making it a bit like an SNRI or a tricyclic anti-depressant category drug, and therefore it may add some particular benefit for the management of neuropathic and central centralization pain disorders. Challenging, however, of the special features is its accumulation with repeat dosing. And that we can see that the initial half-life, though prolonged is far different than the half-life after an extended period of time, going for maybe a 1/2 day to a 1-1/2 or 2 full days to 2 days to 3 days to achieve steady state. It is also highly lipophilic and highly protein-bound, perhaps accounting for its increasing potency as the dose rises. And we'll spend a bit of time going over that. And it's also a factor in that it inhibits its own cytochrome metabolism by revving up those cytochromes. It increases and also inhibits its own metabolism producing the challenging algorithm I've laid out for you on the right, that in under 20 milligram methadone dose it's about a 4-fold multiplier of morphine.

And as we go up it becomes 8-fold then 10-fold, and then 12-fold, which to many of us primary care providers is quite a surprise, since this is not part of the common education that any of us receive. So that when we're giving 60 or 80 or 100 milligrams of methadone we're equivalent to a morphine equivalent

dose of up to 1000 milligrams of morphine, which when we make those conversions is, for us at least, should be a sobering event. What are the indications? Pain treatment, absolutely, and this talk is certainly not to discourage its appropriate use for pain treatment. It has the advantages listed. And likely for Medicaid the advantage, and hence its recommendation for states that are struggling with this very expensive population in this setting of difficult economic times, it's a very inexpensive drug. For addiction treatment, as most of you probably know, it is not indicated by any provider that does not have special DEA licensing and treatment support. As a once daily liquid it eases administration. And there is no doubt that it reduces mortality among heroin users so therefore it plays a very important role.

On Slide 28, in comparing here the differences and pointing out the similarities of methadone versus other opioids, again, to just reiterate, it is marked as different from other opioids inter-patient pharmacologic variability. It has an accumulative dosing potency. And as Dr. Paulozzi indicated, is a higher incidence of overdose and mortality. It's called by some a last resort opioid, which in my mind means it's when the practitioner has determined that this patient is committed to chronic life-long opioid therapy to manage pain and should not be initiated for certainly an opioid naive patient, but also not early in the course of determining whether an individual is going to require a long-term opioid management. It's similarities as all other opioids, monitoring is important. It shares the same side effects of sedation, respiratory suppression, the same anticholinergic side effects of all other opioids and the same cardiac risks, in terms of QT prolongation. That is an area of some experimental work right now, identifying which are the worst agents, and we'll spend a little time talking about methadone unique cardiac research. But as a broad class all opioids will share a cardiac potential. And of course, addition and diversion risks still remain for methadone.

So quick morbidity and mortality, this does not challenge the MMWR of course, but there is a 4-point concern as a provider that we need to be aware, for both pain treatment and methadone maintenance treatment, that adverse events typically occur early during the prescription initiation sequence and that speaks in large part, to poor prescriber knowledge at initiation of dosing. We also know, like other opioids that co-prescription with sedatives adds a very significant risk and calling up benzodiazepines in particular, and alcohol of course, but carisoprodol, another drug which has very high sedative issues and will lead to significant respiratory suppression. Respiratory disease of a variety types also increases risk, COPD and restrictive lung disease and sleep apnea, and as I mentioned earlier that QTc prolongation and potential arrhythmia at higher doses, particularly when they're used with other drugs that prolong the QT interval.

As Dr. Paulozzi mentioned, in 2006 there was an FDA advisory that likely deflected the trend, and I have just highlighted this for your review, that it is complex, that pain relief lasts four to eight hours, much different than its half-life, and that it may build up in the body to a toxic level if the amount taken is too high, and in particular, in the last phrase, if it is taken with other medications or supplements. So, a source of concern for all prescribers and that reference is available for your full review.

So what about QTc prolongation? Well we know QTc prolongation is a risk in just older age, and woman in particular, with co-occurring cardiac disease. And notice these are diseases not of a little bit of occasional arrhythmia or a little bit of angina, or a little bit of heart failure, but we're talking about more advanced diseases. So it appropriate to use in patients who have mild to moderate cardiac disease, electrolyte and magnesium disturbances and concomitant use with other QTc prolonging drugs. And as you can see, the list is substantial. It includes a variety of cardiac drugs. It includes all categories of anti-depressant drugs and it includes a broad range of antibiotics that are commonly used in practice, as well as drugs that work on the dopamine access for both nausea and psychiatric conditions. The QT prolongation concern for those of us doing the prescribing are milliseconds greater than 500 is worth considering discontinuation of the drug, based on this risk.

What's also challenging is that we really can't tell from Slide 32 how high a risk of QT prolongation, in terms of matched methadone serum levels, this is the combined (levo) and (dexter) isomer concentration of methadone. And we can see that's it basically a shotgun blast for the different dose ranges, making it very difficult to predict at what dose we may begin to experience, or our patients should experience, and that we need to increase our surveillance of doses. Torsade de Pointes as you can see depicted here on

Slide 33, is a rhythm we hope never to see. And what's interesting on review of the case series and reports available, and Bob Cruciani has done an excellent job and really supplies the literature with a great deal of excellent research, identifies that the dose range of methadone in most of these studies is quite high. Sixty-five milligrams again does not seem like a high dose but when convert it into Morphine equivalents it's up to 780 milligrams of morphine, and the doses were up over 12,000 MED. And most doses were above 250 milligrams of methadone in these case reports, again supporting that we're worried about this, or certainly need to be worried about this at the higher dose ranges.

Drug-drug interactions complex and for the sake of time and people's ability to maintain cognitive attention, I'm certainly not going to read these drugs but this is available for quick reference in terms of what agents you need to be concerned about. For 3A4 inhibitors, that means they will reduce the metabolism of methadone and therefore raise its levels. And these would be, these are considered the

moderate risk agents and I want to call attention to the listeners of a variety of antibiotics, many of which we use quite regularly. Certainly the quinilones and the macrolides used regularly and tetracyline, metronidazole, pentamidine, protease inhibitors and the like, all have a potential to raise effective methadone levels, hence need to be monitored carefully. And again, this is a caution about dose because when you're up on the precipice on the mountain top it doesn't take much more to push one up over the top into toxicity. Hence lower doses are clearly the safe way to go. Other commonly used drugs are associated with 3A4 inhibition, listed trazadone widely used anti-nausea drugs are widely used. Hence we need to be attentive to the drug profile that our patient is receiving as prescriptions for other indications.

Slide 35 identifies a number of less potent cytochrome 3A4 inhibitors. They may raise methadone level and we again need to pay some attention and you can see a whole range of the drugs we use as antidepressants and the typical antipsychotics. Notably also, grapefruit and grapefruit juice is a factor and even some naturopathic agents may play a role in raising methadone levels. Again it's not quite clear and just caution is raised in this group.

Interestingly, in Slide 36 we can see when we give our patients rifampin they report less adequate methadone effect, is indeed because these induce the metabolism methadone through induction of 3A4 and there will often be a need to dose increase your patient in order to maintain analgesia. And this is relevant often in the chronic pain population, certainly for carbamazepine and in the epileptic population of neurologists for diphenylhydantoin. And when patients who for instance have spinal surgery and end up with complicated wound infections may require rifampin and again concern may be raised by the patient that they are receiving inadequate analgesia and they do have a reason to report that. There's a listing here that I've provided of other drugs that have been reportedly associated with Torsade de Pointes. There's no specific interaction with methadone other than that these also may raise the rate and these again for your reference should be used with caution.

And again we can see the macrolide antibiotics and again the - several of the not so commonly used antipsychotics, but those drugs also have been associated with Torsade de Pointes. So what are the general side effects and concerns that we may have to confront when prescribing methadone? I mentioned earlier that it generates anticholinergia, which is seen with all opioids to varying degrees. Patients will typically gain weight, they will typically sweat, there will be expectation of somewhat reduced motor coordination, and arguably and dose related and based on tolerance, a variety of potential of cognitive impairments. This again would be referent to all opiates as well.

We also know for all opiates they reduce sex hormone release, so we can expect men to reduce testosterone and women to have menstrual disorders related to this effect. And often in clinical practice, certainly I do, I measure testosterone levels in men to identify adverse risks related to libido, sense of well-being, and in fact pain may even be elevated with reduction in sex hormone.

For pregnancy, methadone at this point is recommended to not change and as I've put in yellow for an opiate addicted pregnant woman, methadone maintenance is the standard of care. So dose reducing an individual off methadone at the time of a pregnancy generates a risk of premature labor or miscarriage, greater than the risks associated with managing however gruesome it is and unfortunate it is in neonatal abstinence syndrome. And again, those of us prescribing during the third trimester there's an increased volume of distribution and hence it's common to require increased dose during that stage of pregnancy.

So for methadone dosing, once again go low and go slow, that's the mantra of many of the treatments we use in pain particularly those that are psychoactive. Dr. Paulozzi mentioned the dose recommendations FDA up to 30 milligrams maximum and we'll talk a bit about why in a few moments. But a starting dose, and this would be again though it can be used for an opiate naive patient, it is not recommended for the reasons that should be obvious by now, it is a tricky drug and that once you're committing your patient to methadone most pain experts would recommend that this is the time when you're going to commit for lifelong opiate substitution. And therefore they will be on another drug. I will frequently titrate in methadone at the 2.5 milligram, it's available, it's a 5 milligram tablet at half of the 5 milligram tablet BID initially as I begin to rapidly remove the other opioid during a transition from another opioid.

Again the increased frequency of dosing should be at a prolonged interval at every five to ten days and many practitioners, myself included, will recommend weekly visits during an upward methadone dose titration so you can give your patients just the right amount so there's no temptation for them to take more than recommended because they will not be receiving adequate analgesic response until they get to a steady state level which as we saw can take up to that five to ten day interval.

Again in opiate naive patients I would not recommend it. There is certainly a risk of an accidental overdose when a patient's not tolerated. And per the FDA advisory, I've extracted this quote, "The use of methadone is indicated when pain is not improved with other non-narcotic pain relievers." And I will also add in my own personal recommendation that this would not be a first line opioid to choose when selecting an opioid for management of chronic pain. When there's age or disease related metabolic adjustments, one must always go slow and then the issues of drug-drug interactions need to be paid careful attention to in dosing as I indicated in the earlier slide.

At Slide 40 now, the Veterans Administration, Department of Defense really in my view have one of the finest and most detailed clinical practice guidelines. I've referenced it to you for there, one can Google that and get to their site pretty readily. The dose increments again are supported by what I just described of 2.5 milligrams. And their recommendations are up to every 8 hours and the increases are done every five to seven days and if there is no problem with daytime sedation. Note again the broad interval of time before dose increasing per their recommendations. And again stating as I mentioned in my opening that the half-life of the drug is longer than the duration of the analgesia, hence the common question is why don't we just dose this long acting drug once a day or twice a day, is that the clinicians experience with this drug for analgesic response appears to be more effective at Q8 or Q6. That in other words, three or four time a day dosing.

In the state of Washington, if you recall from Dr. Paulozzi's slides, we are up there with the high dosage, we're up there with the high opiate deaths, and I believe Washington State was one of the first that had opiate overdose deaths exceed motor vehicle accidents. And there's been a big effort in this state to improve provider education and increase the safety of the use of opioids. This is an (Excel) version. You can go to the agency medical directors group and get access to a web based version that you could use on any hand held device. The state of Washington identifies a threshold dosing of 120 milligrams before specialty consultation is expected.

And this again speaks to Dr. Paulozzi's earlier comment that 30 milligrams is considered a high end dose for methadone and if the conversion is four, 30 times 4 is 120, so we're all talking the same numbers in my mind supporting the fact that this is a very robust recommendation. I filled in some numbers on this calculator to again reinforce that at 80 milligrams of methadone for instance, if you can follow that chart that I've outlined on the slide, you can see you're up to by using that conversion at nearly 1000 milligrams of morphine. So the calculation certainly does play a significant role in our ability to manage. And here's a blow up of the rationale for those dose issues because you can see at 40 milligrams a day you are up to 320 milligrams of morphine equivalent dose. Again, considered by many to be a dose that may - the risks may exceed benefits.

So for converting patients from methadone, onto methadone excuse me, from morphine, and this again is outlined in detail in the VA/DoD guidelines. Calculating the equianalgesic dose, you would go to, at most 50% to 67%, many of us would pick even a lower number, as low as 10% of the calculated equianalgesic dose due to the variability of patient response, that the dose calculation varies with the total dose as I indicated the dose has an accumulative potency. And again the dose is proportionately dependent on the morphine equivalent dose of the previous opioid. So it's a bit complicated but using a morphine equivalent

calculation going to, my recommendation, no more than 50% and I would typically choose between 10% and 50% of the morphine going into the methadone dose choice.

So in a nutshell, above 200 milligrams, it would be 5 milligrams q8. And again in an opiate tolerant patient, in the higher dose of morphine range of 200 to 500, again picking 5% to 10% of the oral morphine equivalent dose, divide that by 8 and so that gets us again within the numbers that were described earlier. And I would urge that if your morphine equivalent, if your patient's morphine equivalent dose is above 500 milligrams per day, that's probably the time you're going to want to get some help to make these conversions because it is again not for amateurs.

So a summary here now, I brought together a number of studies incorporating the DA guidelines and some publications that are cited elsewhere that a rotation again is at the 10% to 15% of the morphine equivalent dose. And an important note is that if the previous dosage of opioids are ineffective, this may overestimate the chosen methadone dose that the analgesic effects can take days to stabilize, that the conversion ratios again are not bi-directional. These equivalent doses are very rough numbers without a lot of clear science to allow us to have a high degree of confidence that they're accurate and I round them to the nearest 10 or even, in some cases, the nearest 50 when we're dealing with methadone. And that the formula based on the morphine equivalent dose should be the dose taken at the time of the switch. And again for about the fifth or sixth time, repetition never hurts you, that the potency rises as its dose is increased.

In terms of risk monitoring, Slide 44, it's the same as other long-acting opioids. Opioids are all high risk drugs and Dr. Mark Sullivan here in Seattle has recently published a very interesting review and we're experiencing it in our clinical practice here at the University of Washington, what he describes as, oops, I have misspelled it, it should the principle, P-L-E, of adverse selection in that the highest doses of opioids of all categories are being given to our highest risk patients. And those high risk patients are high risk in terms of co-occurring substance use disorder and co-occurring psychiatric illness. And if you subset out these patient, those are the patients that are getting the highest risk drugs, receiving one of our highest risk agents. Chronic opioid therapy risk is also best evaluated prior to the initiation of the chronic opioid therapy and you can select which tool you'll use.

At the University of Washington we're currently using the opioid risk tool but the SOAPP-R or the DIRE score, some measure of risk before you embark on a long-term opiate plan for your patient is very important, so you can evaluate whether the benefits of opiate therapy are going to be supported by the risks associated with patients in particular who are at high risk for other issues.

Next Slide 45 is the screen shot of Lynn Webster's Opioid Risk Tool. It is in the public domain. I got this off the internet a few years back. It's simply 10 questions and off this you can get scoring which is in yellow, low, moderate or high. And that in my practice has been a good launch point for a conversation with a patient that this may just be too high a risk drug. And the analogy I would make to clinical practice is, I'm not sure I'd given an NSAID to a patient with hypertension and congestive heart failure. And my conversation with the patient would be that you represent, due to your other conditions, in this case risks, represent too high a risk patient to be using this high-risk drug. It's a very useful strategy and then again in Washington State our guideline recommendations identify urine drug toxicology for adherence monitoring to be based on the risk category. So as you can see on the left, the risk category - low risk, moderate risk, high risk and the urine drug testing frequency that's recommended.

So if you're a 65 year old patient who's taking a low-dose opioid to manage osteoarthritis with low risk of abuse or mental health disorders and a high degree of adherence is someone for whom up to one year is adequate on urine drug toxicology monitoring. And that those patients who are at high risk and certainly with any of the behaviors listed are recommended to have very frequent urine toxicology monitoring. And frankly again, a high risk drug with marginal benefits because opioids in long-term use may not be more effective than 30% reduction on average of pain intensity, may be more risk than the benefit they can support.

Urine test monitoring on 47 again is a little different for methadone than the other opioids. The point-of-care testing are generally reliable, however, in a number of studies we have between 20% and some studies up to 40% false positive results on the point-of-care urine monitoring based on the antibody to a variety of metabolites and the cross-reactivity of that antibody. And hence it is an issue for interpreting what's going on in a patient in who you have a surprise result. And you can see false positives are seen in a response to a number of fairly common drugs. Diphenhydramine, your patient may be taking over the counter in a sleep aid or for their allergies, verapamil, and your patients who are receiving psychiatric care might indeed be on quetiapine as well. So you may have false positive methadone on point-of-care.

So the confirmation testing by liquid chromatography or gas chromatography when the results are unexpected and the patient does not admit to those drugs. It's a very expensive test. It'll be about $400 versus about $20 for the point-of-care and therefore getting a confirmation on every patient, and when the patient says, well I really did use that drug, it does not appear necessary to spend that additional resource dollars on confirmation when you're simply confirming what the patient's already admitted. You can request reflex confirmation when you inform your laboratory of what you're expecting and this can be done reflexively. And there are a number of adulterants available on line and our sophisticated patients

certainly know how to find what these drugs are that can interfere with the assay. Adherence monitoring, I want to just begin to close my conversation here with that there are available solutions. Dr. Paulozzi mentioned the prescription monitoring programs and we thank the states for support.

Washington State as you can see in the top left corner does have a PMP on board. There's, essentially all 50 states and territories are currently ready to operationalize the ability to capture all prescribed, even cash purchased. It will not, however, capture illegal distribution of this drug so we're not off the hook by just inquiring prescription monitoring programs. Many states also are initiating emergency department information exchange. There's dated support of substantial savings to patients when systems introduce emergency room to emergency room to provider conversations that may allow the provider in whichever setting to identify no controlled substances. And the case manager can then move the patient through a system of informing the primary care team of what's going on.

And here's the reveal of the rest that didn't appear in the slide. So there's a registration process and then a message to the primary care office that something's awry in the patient's behavior to emergency department. A number of co-occurring conditions that we need to be aware of and a number of screening tools are listed. The UW has an accessible pain tool kit which I'm happy to share with listeners to gain access to all these measures that are described, for sleep apnea, for depression and anxiety, and post-traumatic stress, for drug-drug interactions by reconciling or sharing an electronic medical record system.

And then the question of cardiac monitoring remains a question and Dr. Cruciani and others still say, to EKG or not to EKG, it is still a question whether we do that on all patients. In my experience, we do not do that here at the University of Washington unless there is a concern about pre-existing or other drugs that are on board. So tapering methadone is a bit challenging. Our efforts have been to traditionally reduce by 10% per week using clonidine. It's listed in a number of guidelines as you can see. This is often challenging for patients and in the bottom bullet, dropping down and stabilizing at a lower dose may be necessary and even reducing the previous rate is outlined.

I'm not going to spend a lot of time here and there may be some questions on how we can best taper, but even though it is a long half-life, patients do not do well typically with opioid dose tapering, particularly as you can see on one of my closing, near closing Slides, 51. That if the patient has a substance disorder as a significant concern, there is a very high incidence of relapse onto opioids and therefore referral to a methadone maintenance or other opiate substitution program may be best advised. And after a long epoch of high-dose use, patients will frequently destabilize even without an established substance use disorder, based on what we're describing here in Seattle as an opioid, a persistent dependency syndrome

where patients begin to act like addicts even if they don't meet substance use disorder criteria. Their schedule may need to be protracted with frequent plateaus based on clinical response and in all circumstances a behavioral health support is necessary.

So in conclusion, methadone is an effective analgesic and should be prescribed for carefully selected patients. This is a very important cost benefit and in an era when we're very cost conscious about how we're going to be able to afford a shrinking budget for managing complex patients. Its analgesic interval is shorter than its half-life. It has huge inter-patient variability. Its dosing is complex with an accumulative potency. There are a number of drug-drug interactions and metabolic interactions which must be attended to and relevant to many primary care practices. But when used carefully, and hopefully this brief overview, will bring you up, not quite to expert standard, but you'll be a bit less than an amateur now at the end of this conclusion since methadone is an effective and safe medication.

Thank you for your attention and I believe now we're going to be ready to take some questions.

Loretta Jackson Brown:
Yes, thank you, Dr. Paulozzi and Dr. Tauben for providing our COCA audience with such a wealth of knowledge. We will now open up the lines for the question and answer session and as always, you can also type your questions through the Webinar system by clicking on the Q&A tab at the top of your screen. Operator.

Operator:
Thank you. It's star 1 to ask questions on the phone. Please unmute your phone and record your name. Star 2 to withdraw your request. Once again star 1 at this time. One moment please for the first question.

Loretta Jackson Brown:
Okay, and while we're waiting for the first question from the phone, we do have a question through our Webinar system. And the question is, "Is methadone a preferred lone acting medication for a chronic narcotic? Why? And if not, which medication is preferred and why?"

David Tauben:
Okay, let me take that because in my conversation I just concluded I would not consider it the preferred long-acting methadone, excuse me, long-acting opioid in chronic pain based on the complexity that we see and the associated documented epidemiological consequences of the widespread use for pain.

However, it is a very reasonable choice for chronic opiate therapy in many patients who have not benefited from other opioids or who have other peculiarities of their case, for instance, cost, they can't afford these other drugs, or it's unique NMDA antagonism and other potential enhancements of analgesic response, but I do not use this as a first choice drug and it's certainly not a drug for the opiate naive.

Loretta Jackson Brown:
Okay, thank you, Dr. Tauben. Operator do we have a question on the phone?

Operator:
We have one question on the phone. (Sandra) your line is open.

(Sandra):
Calling from California. I really appreciate this lecture. At our institution we're having an increased use of methadone, in particular IV methadone. I was just wondering, I have a couple questions but first, I was wondering if you're familiar with any increase that QT prolongation with the use of IV methadone in respect to this preservative causing the increase in QT prolongation?

David Tauben:
Having just reviewed that (Sandra), it's a good question. IV methadone is a very reasonable alternative to other IV agents. And again it's in an in-patient setting presumably and therefore the monitoring and concerns about other drug-drug interactions will be front and center. It's conversion to IV morphine is about one to one in terms of its use in that setting. There is reports of QT prolongation in the large studies that have been published. It's described as one of the causes for QT prolongation but it does not stand out as one of the unique factors that's associated with QT prolongation. It's only identified in a handful of studies that report this problem and I do not know anything about the preservatives that might be associated with that and my expert guess on this in clinical judgment would be, it's not the preservative it's the dose and the accumulative toxicity in the setting of other drugs. Often in an in-patient setting, patients are receiving sedative agents and possibly drugs used for psychiatric treatments and these do have significant drug-drug interactions. And as a general rule, I would never prescribe a benzodiazepine of any form unless there's a strong and absolute requirement for that in the patient receiving IV methadone, again, based on its risks with respiratory suppression.

(Sandra):
I really appreciate that. My second question is, we have a large number of our anesthesiologists who are,

I'm calling from an in-patient setting, who are using IV methadone in acute pain treatment, particularly peri-operative in the ORs, they're giving them IV methadone doses and then in the (PACU) when they come out for 24 hours they're using IV methadone. And then just basically for 24 to 48 hours and then just stopping them, and after that they're not continuing on it. Have you seen or experienced or have any experience with IV methadone (for a QT)?

David Tauben:
Again in the setting of a hospital-based practice that would be reasonable and every hospital will have its own culture and formulary requirements. It's a very effective analgesic. It has a nice durability of half-life and in the acute setting for a couple of doses to stabilize a patient seems reasonable. And there's also a prolonged duration of time before the drug clears, so there may be some carry over into the next couple of days of the hospitalization reducing (PCA) requirements. That is a downside because other drugs may be added and other opiate management may make it more complicated but I don't think there's a special red flag that goes up in response to their use and it would reflect the same practice approach using other opioids.

(Sandra):
And then I'm so sorry, I have one last question. This is particularly to monitoring and we are having some problems at our hospital in terms of putting into policy and procedure how to monitor especially for the cardiac side effects of methadone. And from your lecture I hear it's kind of inconclusive how everyone is doing it and I guess at your University in Washington you guys are really not doing EKG monitoring on the patients. Even on high dose patients you guys still don't require EKG monitoring?

David Tauben:
No, no, that's not correct. That's a good question. There's no clear cutoff for when - or top end which time one would start monitoring. Certainly if you're going above the 30 milligram methadone dose you're putting your patient at risk simply for a lot of other reasons and an electrocardiogram would be very appropriate if a patient's on other QT prolonging drugs and, as you can see from the earlier slides, there are a number of them, I would recommend getting an EKG. The question that's begged is, for every patient that you're going to initiate methadone on, must one get a pre-treatment EKG? That's clear. The data is not at all certain as to when to proceed but I would recommend doses above 30 milligram would be a very reasonable time to introduce EKG monitoring for the QTc prolongation. And again, methadone is not unique in this category. All the opiates seem to have - they're not all documented yet but many of them do have QT prolongation and it may be a class effect rather than just related to methadone. And the issue is methadone has been dosed at such high levels historically that it appears to be predominantly a

dose-related phenomena.

(Sandra):
I really appreciate your time and your lecture was very well put together and very informative. Thank you.

David Tauben:
You're welcome.

Loretta Jackson Brown:
Operator, are there any more questions over the phone?

Operator:
Our next question comes from (Sally). Your line is open.

(Sally):
Okay hi, I have a question. If a patient is stable on methadone and the doctor wants to convert to morphine, what is the best way to do it? Do we (BC) it, cold turkey, or do we taper the methadone off and then start morphine slowly up and, you know, the ratio between the two are variable so I don't know what the best ratio some source has two to one, three to one, eight to one, it depends. So what is the best way to taper them, to switch them?

David Tauben:
Okay, I'm going to go backwards on that. I'm not sure why anyone would go from methadone onto morphine. So generally speaking, if one's going to do a rotation it would be a rotation on to methadone. If the patient's having an intolerance to methadone and one needs to come off, it is a, as you identify a tricky conversion and one can use the morphine equivalent calculator to identify sort of an approximate morphine equivalent dose. And then any conversion I would certainly use the 10% of what that morphine equivalent dose is before one even begins to substitute in morphine. The other issue is that the methadone will be biologically active due to its prolonged half-life for seven or even ten days. And therefore the up-titration of the morphine, for instance, would need to be staged in slowly. So it is not a typically recommended approach and many of our community providers in Washington State are frightened by methadone because of the scary data that we see. And the question is I've got a patient doing really well on 20 or 30 milligrams of methadone. I've got to get off methadone or morphine. And we say why? The patient's doing well, they're stable. Doing this conversion exposes them to increased risk. It's not clear to me why anyone would want to go that route. I'm concerned about the amount of time we

may have on the further conversation. And let me propose, Sally, that if we want to go through some of these numbers more precisely, I'd be happy to do that through a separate conversation that won't consume the group time currently.

Loretta Jackson Brown:
Right. And if you have additional questions and we run out of time you can please email your questions to coca@cdc.gov and we will get that question to our presenters today. I have a question here perhaps for Dr. Paulozzi. This one is, "Are we in an era of excess narcotic prescribing and if so, why?"

Len Paulozzi:
Well I think the pendulum has swung towards much more liberal use of opioid analgesics for pain in the United States from the situation that we were in let's say around 1990. Through 2010, rates of the use in the United States have continued to go up and of course we're seeing the consequences of increasing use in multiple outcomes, not just drug overdoses. So I think that there's certainly some indications that in some places, with some patients, under some conditions we are using too much opioid analgesic, that we might have done better with other modalities of treatment of pain and spending more time thinking about non-pharmacologic approaches to managing pain. The other question is why? Well, it's the availability of new products, changes in attitudes of health care providers, increasing rates of non-medical use of the drugs driving further prescribing. It's kind of a snowball effect over the last ten years of misuse leading to additional prescribing and more ambient levels of drugs in society, the more is available for diversion and people taking from friends and relatives left over drugs in the home. So it's a complex situation that many social and clinical factors have combined to create the highest use of opioid analgesics of any country in the world.

Loretta Jackson Brown:
Thank you. And Dr. Tauben, I'm going to combine two questions from the Webinar system. And one has to do with positive urine drug screening for marijuana in patients who are also taking methadone for chronic non-cancer pain and how do you look at those drug screens as well as methadone being used safely in patients with cirrhosis.

David Tauben:
Okay, well let me, that's good that's, let me do the second question first. The answer is it's a risky proposition based on the principle hepatic metabolism. So that would not be a recommended choice of opioid. One would pick one that has a more balanced excretion and pattern that would include urine excretion, I'd pick long-acting morphine for instance which isn't costly. But I would not use methadone in a

patient with cirrhosis. The earlier question is a lot harder. It almost requires a Doctor of Jurisprudence, not a Doctor of Medicine to answer, and perhaps at a national level. But the DEA restrictions on prescribing opioids in the setting of the known illicit drug use does come into effect. So if in your state medical cannabis, or marijuana, is not allowed, the use and finding of marijuana in a urine test would indicate clear illicit use and therefore there is some risk by the provider to provide any opioid. In Washington State it's more confusing. Washington is a state that has permitted with, under our administrative code, a legal use of cannabis for certain set conditions. And in this setting we consider cannabis, if it meets criteria, a legal drug. And therefore, one is not encroaching DEA restrictions on its use. And so I would number one, in conclusion state it is really a state by state decision. And again it's a provider by provider decision. And in our clinic for instance, several of our providers consider use of medical cannabis a contraindication for any opioid. And other providers who I admire and respect, and I would include myself in this group, I will prescribe an opioid in the setting of medical cannabis but I will make certain I understand why the patient is using cannabis, for what purpose. Are they relieving anxiety and distress? And perhaps to be better means that are non-pharmacological and other strategies other than the reliance on medication that they've chosen that may have other psycho-active effects. So it's a very complicated question and it requires number one, an analysis of your state policy and then your own clinic operational policy as to its co-prescribing.

Loretta Jackson Brown:
Thank you. Operator, do we have another question from the phone?

Operator:
Dr. (Lyon), your line is open.

Dr. (Lyon):
Thank you, great presentation, really enjoying it. You had responded a little bit earlier to a question regarding the use of benzodiazepines and concurrent IV methadone use. I wanted to go back to just PO benzodiazepine and PO methadone use. Would you feel that they are also contraindicated there?

David Tauben:
Actually it's a great question and I would say it is a relative contraindication, a relatively strong contraindication. But there are certainly circumstances in which benzodiazepine's oral and oral opioid including methadone are indicated. It needs to be with great degree of caution. And I'll quote one of the medical students who works with me, he says, "Well you keep telling me, Dr. Tauben, that we're not supposed to give opiates with benzos and why are all of our patients coming into this clinic on opiates

and benzos?" And therein lies the rub, that it is very difficult for most providers to manage anxiety. And since anxiety is such a co-occurring disorder with chronic pain, it is a difficult challenge. And this is where non-pharmacological strategies are extremely valuable, getting your behavioral health team on board, learning how to manage anxiety with other strategies. And I would typically recommend in this circumstance a formal psychiatric consultation to see if there is another strategy that might be effective to control the patient's anxiety which would be driving typically the requirement for benzodiazepines. But it is a yellow, orange, red flag alert. Doesn't mean we don't do it in clinical medicine. But it would be an exception rather than any common practice approach.

Dr. (Lyon):
Thank you. I have a follow up for that. I am at the VA. There are a significant number of patients with Post Traumatic Stress Disorder and chronic pain who are on benzos and methadone or other opiates. And it becomes a very, often confusing situation as to how to treat these comorbidities, especially with such a potentially dangerous combination.

David Tauben:
I agree. And the veterans have a unique challenge in this. We see a lot of PTSD in a variety of other civilian situations. So we're confronting this both at the Seattle VA and here at UW. And our approach has been generous use of prazosin as an urgent blocking aide. And we titrate up until nightmares are limited and the patient reports adequate sleep. We dose patients up over 20 to 40 milligrams of prazosin for PTSD management. And typically in that setting we are able to if not eliminate benzodiazepines completely, can lead to a substantial dose reduction in the benzodiazepine. So that has been one effective strategy. Administration of other psycho-active drugs that are less sedating in the antidepressant category, recognizing that QTc becomes an issue here. Also, it becomes part of the therapy, but most importantly cognitive behavioral therapy, relaxation, mindfulness, and other strategies other than benzodiazepines are our target.

David Tauben:
By no means, Dr. (Lyon), am I implying that this is easy or that we're going to succeed in all cases, but it is really worth careful attention to this factor. And we spend a lot of time focused on getting the patients off the benzodiazepines. And many times that we will not do anything about the high dose opioids and focus first on getting the Benzodiazepines stabilized onto, not the short acting but the long acting agents at the lowest possible dose before we even begin to tackle the other projects. But prazosin has been a very effective drug for this and I don't know if this is (listed) approved indication or not and, I will state that to be certain to check to see if this is a recommended or just a clinical practice that's commonly used

approach in use of this drug.

Dr. (Lyon):
Very good. Thank you.

Loretta Jackson Brown:
Thank you. Dr. Paulozzi, can you comment on MMWR article in February that discussed utility and results in reducing overdose from increased access to (narcan)?

Len Paulozzi:
Sure, yes. There was a national survey of naloxone programs that provided naloxone to people for community use to, for treatment of acute heroin and opioid analgesic overdoses. And a number of programs such as Project Lazarus in North Carolina and physicians at Fort Bragg have started implementing co-prescribing of naloxone with opioid analgesics so that the individual and more importantly their family have access to and training in use of naloxone in case of an overdose. I think that this is a promising strategy that is growing across the United States. There are issues in terms of the availability of a nasal spray formulation of naloxone, which appears to be the easiest one to use. And there are general issues as to which patients is it appropriate to co-prescribe naloxone with. The suggestions in the data of course is that the drug at higher risk include drugs like methadone. And patients that are at high risk are those are taking high daily doses any opioid analgesic. And so those would be the highest risk groups. But, the approach is under investigation, people are studying it. We know that it's being done, naloxone use is being reported in a number of overdoses. And we hope to get additional information that would allow and evidence-based recommendation as to when co-prescribing or distribution of naloxone would be appropriate.

Loretta Jackson Brown:
Okay, thank you. Operator, we have time for one more question over the phone.

Coordinator:
And showing no questions on the phone lines.

Loretta Jackson Brown:
Okay, well thank you. So on behalf of COCA I would like 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 August 1, COCA call, in the subject line of your email and we will ensure that your question is forwarded to the presenter for a response. Again that email address is coca@cdc.gov.

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

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

Coordinator:
Thank you. This does conclude the conference. You may disconnect at this time.

END