CLINICAL TOXICOLOGY OF NEW DRUGS©--Part 2

SPI WEBCAST

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PEG CAMPBELL: Good afternoon. I'm your moderator for the day, my name is Peg Campbell I'm a certified information specialist from the Poison Center in Charlottesville, Virginia. This is sponsored by the Maternal and Child Health Bureau, HRSA poison control program in Rockville, Maryland. Before we get started I want to give you some instructions to help you with your webcast, experience. If you need a handout, you should have received one in an email that you could print out. You can also go to the website, AAPCC web side and the slide changes are synchronized with the speaker's presentation. You do not need to do anything to advance the slides. You may need to adjust the timing of the slide changes to match the audio by using the slide delay control at the top of the messaging window.

I encourage you to ask the speaker questions at any time during the presentation, simply by typing your question in the white message window on the right of the interface. Select question for speaker from the dropdown menu and hit send. Please include your state or Poison Center in your message so we know where you're participating from. The questions will be relayed onto the speaker at the end of the talk and he'll be able to answer your questions. If we should run out of time, he'll be glad to email you afterwards. We encourage you to submit questions any time during the broadcast. On the rest of the

interface is the video window. You can adjust the volume of the audio using the volume control slider to access by clicking on the loudspeaker icon. Those of you who selected accessibility features when you registered will see text captioning underneath the video window. At the end of the broadcast, the interface will close automatically and you will have the opportunity to fill out an online evaluation. Please take a couple minutes to do so. Your responses will help us plan future broadcasts in the series and improve our technical support. Slides will appear in the central window and advance automatically. The slide changes are sin con iced with the speaker's presentation so you don't need to do anything to advance these slides.

I just read this for the second time. Is there anything else we need to tell you? OK. At the end of the broadcast the interface will close automatically and you'll have the opportunity to fill out the online evaluation. Before introducing our speaker I would like to thank several groups of people. First, HRSA and Maxine Jones for the grant to make the webcast possible. AAPCC board of directors for the continuing support. Rose Ann for her continuing skills and advice. The University of Illinois Chicago for technical support. Don Rasmussen and their staff and Jean coal did a lot of work to get this initiated.

I would like to introduce to you Dr. Edward P. Krenzelok who is the director of the Poison Control Center at Children's Hospital of Pittsburgh and professor of pharmacy and pediatrics at the University of Pittsburgh. He has served in this capacity since 1983. He's active in 14 professional toxicology and medically related societies and associations and a past president of the American Academy of clinical toxicology. He's the chair of the

clinical toxicology and drug expert committee. A former member of the food and Food and Drug Administration drug advisory committee on the panels of numerous medical juniors and the author of several hundred scientific chapters and editor of two books. With all of that and that actually is not enough because I've heard many more things about him and all positive, we welcome Dr. Krenzelok.

EDWARD KRENZELOK: Thank you very much. It's a pleasure to be here. I would like to extend my thanks as well to Maxine Jones and HRSA for organizing and sponsoring this. To Jean Cole and the committee for inviting me to speak today. I'm honored that you asked me to speak and it is really a pleasure to be here. Pleasure to be here for a number of reasons. Number one is prior to asking me to speak about these things I was really in the dark about these drugs so I've really learned a lot about them as well. So in some cases I may be a page ahead of you and in some cases you may be a page ahead of me. I'm sure our knowledge base won't be too far different given these are all new compounds.

Compounds that one of which we have seen introduced in the clinical practice just in the last month. Others on the verge, perhaps, others have been turned down recently. So they're all things that we may get calls about in Poison Centers. Let's take a look -- by the way, I would like to say a hearty good morning to those on the west coast and throughout the Midwest and, of course, good afternoon to you people that are participating in this on the east coast. On the next slide we see that there are a number of drugs and this part two of the new drug clinical new drug webcast I've been asked to discuss. Two weeks

ago on August 10 Wayne addressed a number of drugs and I'm doing about six more. So you have a pretty good feel for some of the new drugs again that are on the forefront of things that we may have to respond to when a parent, physician, another healthcare professional, someone calls us about these. You'll see these are interesting names that may look somewhat familiar to you. Duloxetine and Reboxetine you may think of as being related. They're related more structurally than -- you probably recognize as a Tolrestat, may be one that is totally new to you. Viloxazine which has been around for quite a while. Next slide.

So how did I approach this? Well, when Jean called me back a few months ago and asked me if I would do this I thought I would be more than delighted to do this. Where is the information? What type of information is available? Where can I find information? First of all I did a little bit of searching and I rapidly discovered there was very little toxicology information available. Acute overdosage information there wasn't very much. There wasn't very much information on pregnancy, for example and at the time when I was asked to do this, only -- none of the drugs were approved and only recently has Duloxetine been approved for use.

One of the first things that I did was to go to the FDA website. You can see it in the central part of my slide. This is a very handy place to turn if you are faced with a situation wondering if a drug has been released, where it stands in terms of its release to the public. Click on the website and it can help you out. The URL is on the bottom line of the slide and that's in your handout, of course. It really gives you a full catalog of drug

products that have been approved by the FDA. Next slide. So as we look at this particular website from the FDA and look toward the middle of it you'll see that there is actually sort of the upper middle part of my slide, actually gives you what the webpage looks like at the FDA. At the very bottom in the middle you can see drugs at FDA. Click on that and it will give you a wealth of information. I encourage you to look at that in advance of having to respond to a poisoning emergency, certainly, but at minimum if you do have a poisoning emergency, you can't find any information on a drug, you're wondering if it's an approved drug in the United States go to the website and it will help you right away. What are the other sources?

You're looking at these we're spies, we know all these resources are available to us. But a mistake that I've made many times, my staff and other centers is gee, they come to me and say it's not on Poisindex and I said did you look here, here and here? And what I've found over the years and even in this exercise looking at these particular drugs is that it's not in Poisindex it may be in Drugdex. It has a wonderful compilation of drugs in the mill in the United States, drugs already approved in Europe or elsewhere abroad, perhaps in Canada. You might find some very good information to help you manage a poisoning emergency based on Drugdex. Something as simple as Google. We need to have very, very fast information, don't we?

So go to Google, understanding that the quality of the information that you may receive could be questionable but you may find a lot of information. I was -- I found that actual Google was very helpful to me in gaining rapid access to information about some of these

drugs. Medline is always available online. Everyone knows how to navigate through Medline. It may not be as fast as you would like it to be. There may or may not be an abstract. You may not have access to as much information as you would like and it may not be as expeditious as you would like it to be. I'm an old guy and I like books. I look in things like Merck and Martindale and a lot of times they have information there from the use of these particular substances abroad that certainly precede their introduction into the United States. These are some resources you can look at. Certainly not a comprehensive list but my quick list of where I go when I'm trying to find basic new information. Next slide.

Well, the other thing that I did was I wonder if we can get just a little bit of an idea about how many times Poison Centers have called -- how many times people have called Poison Centers to get information about these particular compound. How many overdoses have there been? I had two people pull the data from the beginning of test until the current time to see how many overdoses, how many exposures there had been with the compounds that I'm going to discuss today. And you can see there were a sum total of 20. So we know that these are compounds where there haven't been very many calls. There isn't a good experience base. I was hoping there would be a compilation of some of these and give me a -- allow me to develop a better profile on the toxicology of these particular agents is.

This just confirms the fact that these are very new drugs and so there is a lot to be learned about them, certainly. Next slide, please. So my objectives today are basically five-fold.

What I would like to do is explore each of these drugs and give you a good idea about the therapeutic use and mechanism of action. If we know the therapeutic use we aren't as far in the dark as we were prior to getting the emergency call. If we know the mechanism of action, it may help us to understand what the toxicology might be. Selective inhibitor will give us an idea of what the pharmacology is and extend the knowledge to what some of the toxic aspects may be. I'm also going to try to discuss the kinetics of most of these compounds. I was able to find good information on most of the compounds and kinetics give you good ideas about when a drug is going to peak.

When might you expect to see peak toxic effect? How long will the drug persist in the body? What are some of the other features about it such as protein binding, things that might lead you to decide well, elimination may or may not be good in this particular case? And then, of course, management of the overdose. There is nothing that is really earth shaking when you get down to the management of the overdose. I really have tried to look at these things and say if somebody called me today about one of these drugs, what would I do? How would I approach that and manage that? I'll share with you not so much what is in the literature because there is essentially nothing in the literature except for one of the drugs. This is how I would approach these particular drugs. Next slide, please.

Well, as I talk about treatment on each of these you'll see there is sort of a recurring theme. It's again nothing earth shaking. I think the most important thing when we deal with new substances is let's not get excited about it. Let's do no harm. The creed at every Poison Center do no harm and good supportive care. With those two practices we

can manage the vast majority of all poisoning information and as you do every day in your practice of poison information. What about G.I.D. contamination. It's one of those things that may or may not be effective. I would not remember Ipecac in any of these particular agents for a variety of reasons. Charcoal maybe efficacious. Early information for you, as you know the American academy and European association did the position statements in 1997. Well, the second round of position statements will be coming out this year. They're being published. You probably have already seen the first one on Ipecac and they'll be proceeding over the ensuing months. Ultimately the one on activated charcoal I believe, I'm not sure, I think activated charcoal probably tell us we can use charcoal in one to two hour period after an overdose, not just the one hour window that we've been using.

So that may give you a little bit of direction in terms of the management of some of these especially one of them where the absorption of the drug is delay with food. What we can say about every poisoning we manage is extracorporeal elimination is of no value. Dialysis and so on I don't think has any role to play in the management of these cases. Many cases extensive protein binding. They wouldn't avail themselves very well to extracorporeal elimination. What I did to make it easier for you and easier for me is I tried to categorize the drugs. These drugs broke down into two nice categories. One category and the first group of drugs I'll talk about addresses basically diabetic therapy, then the second group of drugs I'll address are antidepressants.

There is always the quest to develop the perfect antidepressant and I think some of these drugs are efforts to try to improve specificity in the treatment of depression and also to

reduce side effect profiles. Some of them do so quite well. So with that let's turn to the diabetic drugs first of all. These are two rather unconventional drugs compared to what you're used to. You're used to taking calls about the more familiar drugs. These drugs are really totally different from those. They are two new drugs from the standpoint of treating diabetes are on the cusp of tremendous advances in helping to treat people that are afflicted with this disease. Next slide.

Well, here for those of you who love activity relationships, I don't but for those of you who do I want to please everyone. Here is the structure of Alredase is the brand name. The therapeutic uses of this are limited to diabetes, of course, but it's an interesting drug in that it's not a drug attempting to reduce blood sugar. It's not a hypoglycemic drug. It's actually a drug used to prevent the complications associated with diabetes. So for example the neuropathy that occurs, the blindness, retinopathy and cataract formation, this potentially has great application in reducing those very serious complications that make life very difficult for many diabetics.

The typical dose 200 milligrams in single or divided doses. The mechanism of action is an Aldose Reductase inhibitor. The reduction pathway of glucose is not converted to Sorbitol. If we have the hypoglycemic patient this pathway becomes active and we ultimately have a link back to Sorbitol. We remember that from years gone past when it was used in the presence of activated charcoal and we've abandoned the use of Sorbitol in the management of a patient. Now it's reemerged. Anyway, Sorbitol is metabolized down to fructose and you see also it's -- both Sorbitol are big players when it comes to the

development of this sort of this pathology that occurs in the long term effects that occur within the diabetic population. Next slide. So why is Sorbitol so bad and how does it get there? There are a number of cells in the body that don't rely upon influence for glucose uptake. Nervous system tissue, the lens of the eye where insulin is not important. There are a lot of -- in these cells where it's not important, glucose is taken up into the cells and then Aldose Reductase will reduce it to Sorbitol. It's a poor penetrator of membranes. Once the glucose is inside the cell the Sorbitol is trapped in the cell and that's what begins this path onto the pathophysiology we see.

What we see is Sorbitol accumulating in cells and then it makes the membrane of the cell, whatever it happens to be into, less permeable. Being less permeable things like amino acid and potassium can't get into the cell. Sodium is trapped into the cell and we see an osmotic effect where we're seeing fluid come into the cells and all these damaging effects due to the presence of high sodium loads, lots of fluid, basically damaging the cell. This is largely what causes a lot of the problem. So then as the Sorbitol accumulates in very important cells, neurologic tissues, ocular tissues and so on we begin to see problems within those tissues and complications that occur as a consequence of that. Next slide.

OK, what does Tolrestat do? It's best indicated as an Aldose Reductase inhibitor. It blocks the pathway to converts glucose to Sorbitol. In the diabetic patient if we don't have Sorbitol in the cell we won't perhaps have the complications, or as many complications that were due to the Sorbitol. So it's very important that this pathway is blocked. I don't know where it stands in terms of when it will be released, but you may get some calls

about it because there may be patients that have taken an overdose of this or a child who got into it as a patient taking it as part of the phase three trials. Let's look and see if it reveals anything at all. The metabolism is quite rapid. The protein binding is extensive with Tolrestat. There are metabolites that come via the metabolism pathway that have some activity. It's only about 10% of the activity of the parent compound itself. We can see that both renal and fecal elimination are very important with this particular drug. I did some -- some of the reading I did would suggest to people who had renal disease might have some accumulation of the drug but I didn't see anything that suggested that their dose should be modified or that -- anything to believe that they would be at a greater risk, say, if there was an overdose due to this particular substance. Next slide.

So what about adverse effects? Well, this is where we run into the roadblock with most of these compounds in that most of these don't have any overdose -- we have no overdose experience with any of these. I think the best thing we can do in trying to anticipate what you would see in an overdose situation is to think OK, what are the side effects, what are the adverse effects we find in Drugdex or Poisindex, those might be extended into the overdose situation. And that's about the best we can say about that.

There is some evidence, because this drug has been around for a while and been available in central America, South America, Ireland and Italy for a while. And in clinical trials and in these countries where it was released, there were a number of patients that developed significant aberrations in their LSE's. 5% of all the patients developed significant elevations in LFT's and there were three fatalities occurred. This would be

something that we would think about with this particular agent especially in people who have used it chronically if you happen to get that call. Other things that I found to be prominent at least from the literature were dizziness and rash. Can't explain why they happen but they were certainly noted as prominent side effects. In terms of the management on the next slide, of this particular agent, I'll tell you today that if I was consulted about let's say a 2-year-old who happened to get 200 or 400 milligrams of Tolrestat, I don't think I would worry about it at all. We know it is not going to cause hypoglycemia in the child. In effects at all. The risks as I've indicated in the slide, low risk, no risk.

You're saying well, what about the possibility of hepatic necrosis? From the data I looked at there was no indication that hepatic necrosis would occur in anything but the chronic use type scenario. Maybe if a person was on it chronically and took an overdose it would predispose them more, I don't know the answer to that. Would activated charcoal work? It might if you used it in the first hour or two. It is probably unnecessary in the management of overdoses to this compound. Like all of these things it's best to be a little bit on the conservative side until we get a better handle on the profile of how these things will present and what types of symptoms people will have.

Let's turn our attention to the next agent in the diabetic series here. Exenatide. If you tuned into the webcast two weeks ago you heard this compound being talked about, which is Exendin 4. It's an amino acid peptide. Start thinking about that when you say I have a person who ingested some of this. It will be destroyed pretty well in the G.I. tract. There

was a researcher doing a fair amount of research looking at lizard venoms and so on and found a compound called Exendin 3 in another type of lizard. It led him to begin to examine the venoms of other lizard. Extracted some venom and found the hormone, Exendin 4, which decreased gastric emptying after a HILA monster ingested a rodent so it could digest the animal more efficiently. So a lot of research was done and basically it was determined that maybe this has some role to play in the management of the diabetic patient. Next slide.

And I must tell you, too, remember, this is a synthetic compound. For those of you worried about people going out and trapping HILA monsters and killing them to get their venom and so on, have no fear, that's not being done. This is a synthetic compound. All right. What are its therapeutic uses? It's important to realize this product is effective only in people with type 2 diabetes. If you have the juvenile or type 1 diabetic this product won't be efficacious. You have to have a viable pancreas for this to work. It is projected to be a substance that can be used with the other oral hypoglycemic agents that we already have. If you look at the way it's administered, this is not an oral agent. That's an important thing for you to remember. This agent is injected subcutaneously. You can see that the typical starting dose is for 30 days and the slide is in error. It should be five to ten mikes B.I.D. You'll see the reason why when I discuss kinetics if a few moments.

Let's look in more detail about this particular agent. We need to understand, I think, type 2 diabetes. I don't mean to insult anybody and I don't claim to be an expert but it helps me to understand how this drug would work, you know, once I looked into the path and

physiology of type 2 diabetes. It's a combination of two processes going on at once. One would be peripheral resistance to insulin itself. The insulin itself may not be working because there is resistance to it. The other one is a progressive failure of the beta cells of the pancreas. It's a combination of these two resulting in either the inability of insulin to do its thing because of the resistance or the lack of insulin to be able to address the hyper glycemic episode. Keep that in the back of your mind. Let's move on to the next slide. So then type 2 diabetes, even if you're compliant, eventually early in the identification of your disease, you control your diet, you control your weight, you get lots of exercise, as I understand it there will still be a continuum of progression in how the disease continues throughout the rest of your life.

That's where then when people are no longer controlled with diet and exercise and weight control, then they go on to the oral hypoglycemics and may progress on to insulin therapy. Well, what continues to happen, as I've alluded to, is beta cell failure continues throughout the course of this disease, maybe more rapidly in some people than in others, and then the other thing that is interesting is that resistance doesn't progress as fast as beta cell destruction. This drug prevents some of these things from occurring. Next slide.

So what this particular drug does is it basically is getting down to some of the root cause of diabetes. It's basically trying to prevent further beta cell deterioration. To arrest it and even are he verse it. There is some discussion it may actually reverse the trend and you get beta cell enhancement. New therapies in the management of diabetes are sort of looking in the direction of producing synergistic effect with preexisting agents and

enhancing actually beta cell function or arresting it so that the beta cells don't die as rapidly or become dysfunctional. So let's look at how this compound works in the next slide. It's kind of a complex mechanism of action. Sort of like looking at where you have all the different metabolic things going on at once and I wonder which one of these aspects of toxicity will prevail? This particular product is very similar to that. What it will do is five-fold, at least five-fold. It stimulates insulin see -- secretion. It will respond to the high glucose load and allow people to manage that. That's one thing. Another thing is that it decreases high glucagon secretion. We know it's important to that constant high outflow of glucose from the liver.

If you can stem that, if you can basically slow that process down, if you can stop the liver from releasing so much glucose then perhaps you can modify that hyper glycemic response. Remember, I had mentioned some of the early research on this found out that the Exendin actually decreased gastric emptying. This does the same thing. It decreases gastric emptying. You don't have the huge nutrient load going to the small intestine at one time and producing this hyperglycemic event again. It's another aspect that is very important to consider. It also apparently decreases your craving for full. Makes you feel full and hopefully decreases food intact and obviously decreases food intact will decrease the amount of glucose available for absorption and the other aspect of this is it will increase beta cell proliferation. There is evidence it does enhance it. I don't think this is going to be a substance we see very many overdoses. \

Certainly, again it's a subcutaneous injection, not something you take orally. Well, there is not of information available on this product that I could find. Remember, it's a subcutaneous injection. When you inject it, it's fairly bioavailable up to 75% or so. Distribution is not huge, metabolism, I couldn't find anything of consequence. Its half-life is fairly short. It doesn't correlate to length of action in a direct correlation but the length of action on this particular product isn't long which means you have to have multiple injections, two injections per day at breakfast and supper to control these things. Next slide.

So what are the adverse effects and what do we expect to see in an overdose? Well, as I've told you several times now, there are no data at all related to this compound that I could find anywhere related to any type of extraordinary overdosage, whether it be ingestion. One thing I did see is that headache, nausea and vomiting were profound in this particular -- with this particular drug if people did experience a lot of discomforting side effects up to the vicinity of I think around 15%. There was one study I looked at that indicated a 31% incidence of nausea in these patients. So you can see where that may not be a very compatible -- be very compatible with compliance with using a drug like this. But it appears that as this drug is used more and more and more you do become somewhat tolerant to these symptoms.

You're probably asking about hypoglycemia, what if we have an overdose, will it produce hypoglycemia? It will increase insulin release, but I don't think we'll see profound decreases in blood glucose. I don't see that to be the case at all. The only time I was

able to find any information that suggested that mild to moderate hypoglycemia occurred is when it was used in conjunction with others and unclear in the studies whether the hypoglycemia was due to the Exenatide by itself or due to the oral hypoglycemics that appeared. I don't think we'll see profound hypoglycemia like we would with an insulin overdose. Having said that, however, until there is more experience with it I think it's probably prudent to really be a bit more judicious in watching these patients for a longer period of time. Let's take a look at the management of overdose. How do we manage an overdose? Again, my creed do no harm, supportive care and glucose monitoring.

The effects persist only three to six hours. It should give you a good idea of how long this might last. All bets might be off in a significant overdose. You have it where someone has injected 1,000 or 2,000 units of insulin and waiting to be absorbed into the body from the fat pad. I don't know happens to this drug once it gets into the sub cutaneous teep owe if -- depot. I think we're probably -- it would probably be good to watch these patients for a few hours, watch the blood sugars, monitor for other problems and symptomatic supportive care. If it's ingested, and I see only the rare situation where it would be ingested, again remember, it's a 39 amino acid peptide. This is not going to be absorbed. It will be destroyed in the G.I. tract and so you probably don't have the worry about the oral absorption of this compound.

If there is ingestion for whatever reason it may be more important to address why that overdose occurred to determine whether or not this person may have taken any oral hypoglycemics or antidepressants or anything else. I think the Exendin will be the least of

one's worries in this particular type of overdose. That's about the end of the information on the agents that address diabetic aspects. Why don't we turn our attention now to the antidepressants. Normal glycemic, now we've covered that. Now I'll cure your depression. Hopefully I'll tell you that a lot of these things aren't all that toxic so maybe you won't have to worry and be depressed upon the fact they may be coming on the market or are on the market. As I said earlier, business and industry, the pharmaceutical industry is also in search of the perfect antidepressant. No adverse affects and make them like everyone else.

These are four ways trying to find the perfect antidepressant. I'm not sure that any of them are. Our first compound Duloxetine was just approved by the FDA. It's call cymbalta. It says here we have this product just released for the treatment of major depression. This is a very new product only been out for about three weeks and I would venture a guess that most people haven't experienced an overdose at this point in time. Let's take a look at its therapeutic uses. I'll be redundant and say all of these are used for depression. This is one that has a dual action pharmacologically but also a dual action therapeutically. It's used to treat people with major depression.

It seems to have an advantage over other compounds to treat people that have sort of a neurotic component to their depression. Lots of aches and pains and things of that nature. The drug really seems to address those issues as well as the depression, who is to say which one is causing which but it seems to be sort of a multi-symptom type of antidepressant. It has -- this is the only indication I'm familiar with is for the treatment of

depression. It has been studied for some off-label uses, bipolar disorder and urinary incontinence. You might want to take a look at the literature along those lines and it's finding its way into practice to treat children who are incontinent or perhaps adults who are incontinent. Typical doses 40 to 60 milligrams total daily or you can do it in B.I.D. dosing. Doses up to 120 milligrams might be expected. Normal daily doses 40 to 60 milligrams. Not unusual to see doses of 120 milligrams as the upper end of the therapeutic range. Keep that in the back of your mine. When you have the first person who says I took an extra Duloxetine or cymbalta today maybe they're only at 80 or 120 milligrams so they are maybe only at the maximum daily dose. Next slide.

So this is one where it's really important to look into the mechanism of action. It's one that -- as you can see it's call a dual selective mechanism of action. Serotonin, nor -- norepinephrine, a selective Serotonin reuptake inhibitor. There is a selective inhibitor coming down the line, too. There may be some confusion in the early going with this drug and a couple of other ones that have similar abbreviations. Let's think of it as an SNRI. A combination of serotonin and norepinephrine. I know I've fallen victim to this myself. We have an overdose of this new compound. I remember with other drugs is we don't have much information on it.

I suppose it's just like flew ex teen, Prozac, let's treat it the same way and not worry too much about it. You really can't do that with this particular compound. This compound has a different mechanism of action, a dual mechanism of action compared to Fluoxetine. So the slide may be a little difficult for you to see but it should be clear in your handout.

Where does this compound stack up compared to other compounds? So if we take a look at the top of this particular graph you see these are drugs that have a lot of serotonin activity. These are drugs with more add -- this might be a handy little chart for you to use sometime when you're trying to figure out where some of these drugs are in terms of their relationship to other drugs. Next slide.

Now, those of you who tuned in to the last webcast heard Wayne address this particular drug briefly. One of the questions that came up had to do with its sort of met -- metabolic pathways. Let's look at its bioavailability. It's 70% bioavailable. Not all is being absorbed. It's moderately good absorption. There is a two-hour lag from the time it's ingested until you see absorption. In the presence of food it's delayed six to ten hours. The person who happens to take an overdose of this and has dinner at the same time may have a significant delay in the onset of symptoms attributed to this particular agent and the peak absorption of this agent.

Maybe you think about this a little bit in terms of activated charcoal. Maybe it might have a little bit larger window of application in the management of one of these overdoses. The distribution characteristics of it, you can see huge distribution, tremendous protein binding primarily to albumen and Alpha one GLYCO protein. There would be no reason to do elimination. Just for these reasons alone there would be no value. You see that it is metabolizeed by the liver by the enzyme system. This is a question that developed around Wayne's presentation when someone called in was whether or not it inhibited or induced these enzymes. It's an inhibitor of 2D6. That means other drugs that are

metabolized by 2D6, if 2D6 is inhibited, concentrations of those drugs may increase substantially. So let's take a look at a couple of examples that come to mind. One would be the Tri-Cyclic antidepressants. They are metabolized to a large extend by 2D6. If one were taking this drug and a try cyclic maybe you would have elevated concentrations, significant increases in the concentration of the Tri-Cyclic. It's contraindicated. It should not be used for THIRITIZINE. You put high concentrations in people suffering from the cardiac arrhythmias they have experienced in the past and sudden death. That combination should certainly be avoided.

It is also worthy to note this does not induce itself at all. It's just an inhibitor and doesn't induce itself. It doesn't induce either of these enzyme systems. One other note is that people with HIPATIC involvement. If a person would have significant compromise one might want to back off on the dosage. The person who overdoses on this who has HIPATIC disease has a risk of -- The adverse of 12 -- we would see in an overdose. Insomnia we aren't going to worry about. Migraine headaches were common in these people. It's not uncommon in people taking serotonin reuptake inhibitors. What other types of things have been reported? Dry mouth, dizziness have been reported. Cardiovascular effects have really been minimal.

I'm not certain if this drug affects the fast sodium channels like Tricyclics do. It may doesn't and we maybe don't have to worry too much about this drug in terms of tremendous aberrations in cardiac rhythm and so on. That remains to be seen. It's not the case with a lot of the other Serotonin reuptake inhibitor. We'll have to see what

happens as we gain more experience. There is evidence that LFT's may increase minimally. You may want to run a panel that overdose on this compound. Seizures have not been noted in the literature, at least that I've looked at. So there is nothing out there like a smoking gun that an overdose due to this -- involving this will produce seizures. There is very little overdose, direct overdose information. In looking at the package insert from the company you can go again to the FDA website or I know this was all emailed to everybody who is a member, you can find the Duloxetine product information and they reported four non-fatal acute overdoses that were sole ingestions of Duloxetine and a couple more in combination.

Doses of 300 to 1400 milligrams with absolutely no significant adverse events. No fatal outcomes at all in these. It would appear, at least in the preliminary data, this seems to have a fairly safe profile. Time will tell. I suspect that next year at the North American Congress of toxicology will say it's safe or say the information I provided you on the webcast was totally wrong. We'll see next year at the meeting. Let's take a look at the treatment of overdose. Well again first of all supportive care, I think most of our overdose management with this particular compound can probably end right there. However, if you do run into that unusual circumstance where a person overdosed, had a big meal as I said before, absorption is delayed, it's delayed significantly but maybe some delayed activated charcoal three and four hours later may be of value.

Still, my gut reaction is that probably won't help because the drug probably has propelled itself in the small intestine and the two probably won't come in combination. It probably

would not be an unreasonable thing to at least consider because this is a new compound we probably should monitor these people for cardiac toxicity, although I do not anticipate there would be significant cardiac toxicity associated with it. I did see a couple of instances when there was abrupt withdrawal there were a serotonin like abrupt withdrawal syndrome. There have been some -- I couldn't tell for sure. It sounded like there were fatal involving coma when the drug had been used in close proximity to the use of another inhibitor at the same time. I think we should be aware of that. Other antidepressants that are metabolized by 2D6. That's all I have on that particular compound.

Let's move to the next, please. Well, here is a compound, Gepirone that is a PURONE compound. Unlike the previous compound that had just been approved by the FDA, this is one that is not approved by the FDA. On June 24 the FDA did not approve this particular agent for a variety of reasons. And as I alluded to earlier, this is a drug that is very similar to DISPORONE analog. It's an anxiety medication, in combination with other drugs it is one of those front line drugs. It has antidepressant properties but just about every paper I seem to read, except a few that seem to have a bias focused to them. It seemed like the conclusion was this drug didn't offer a lot that we didn't already have. A lot that wasn't available from other drugs.

Whether or not this drug is going to go back through the approval process and be a drug that we deal with. It's possible, but since it has been rejected at least at this particular point in time, I don't think that we'll be dealing with this unless there are people that are in clinical trials that are using it. It is probably not something we'll have a lot to deal with. As

you can see there are two different types of products. An immediate release product where the dose is 10 to 90 milligrams every day and the expended release product where it was 20 to 100 milligrams daily and this is kind of interesting. I'll get back into the extended release product dilemma in a moment. Let's look at the mechanism of action of Gepirone. It is, unlike the last drug that I talked about, which is a dual action inhibitor, this is a pure serotonin 1AAGONIST type drugs. Greater receptive potency. It is one of the factors that led it to be developed. It has left Dopamine receptor findings that BUSPIRONE. It didn't have any effect on GABA receptors. This drug may not have any SNS depression side effects.

An overdose probably wouldn't be associated with -- another factor is that it is not an anticonvulsive. I don't want you to confuse this with another drug that has convulsive properties. It's easy to get them mixed up because they're so close. Next slide, please. I talked about the dilemma of the immediate release versus the extended release products. Apparently the immediate release products cause just a tremendous release of the drug and very rapid absorption and make it difficult to tolerate this particular product. The side effects with the immediate release compound are apparently very significant. The time to peak blood levels is one hour.

That approximates the blood concentrations we see things rapidly absorbed like -- like many of the other antidepressants it takes a while for the properties to kick in. Three to six weeks, maybe up to three weeks for the antidepressant properties to begin to manifest themselves as well. Again, most of these drugs are not take it today and feel better

tomorrow type drugs. They're drugs that do take time to sort of re-regulate in this case your serotonin 1A receptors and up-regulate them so you can reverse the depression. Next slide. So a little more detail on the kinetics of this particular compound. If you look at it compared to Buspirone it is much more available. I could only find information on the immediate release product. I don't know how much better or worse, perhaps, the extended release product is in terms of absorption. It appears to have better bioavailability. It has a large volume of distribution and highly protein bound, again properties that do not make it a drug that can be dialized easy. It's metabolized in the liver and you can see that the metabolite is the same as that of Buspirone.

We're seeing this drug metabolize to the same end product at Buspirone is. There is really nothing very magical about it. Half-life of that active metabolite is seven hours and you'll note interesting differences in the half-life between the immediate release product and the extended release product. The extended release product seems to have a much better profile in terms of its length of persistence in the body and so on. Next slide, please. Well, the adverse effects not surprisingly are perhaps may be an extension of what is side effects. They list drowsiness as a side effect. In the whole litany of side effects drowsiness seems to be in the list of all these particular products.

But from everything I was able to gather, drugs in the depression is not as prominent with this compound as it is with others like Buspirone that are in the Azapirone. Seizures were rare. It's not something that we should be concerned about if we see an overdose that a person should be on a seizure watch. I didn't see anything to suggest that. It's similar to

Buspirone. Since it is close to Buspirone and there were no data that I could find that really detailed the overdose situation, I just thought I would share with you the information that is very easily available to everyone on Poisindex about what the range of toxicity is. What can we expect when we see a Gepirone overdose and can we extend that, perhaps, to -- from what we know about Buspirone? The maximum daily dose is 60 milligrams. Right away it gives you a window of knowledge as to where you are with an overdose. There is information certainly that doses as high as 375 milligrams a day therapeuticly for a month have been tolerated reasonably well.

There was some overdose information, very -- there were some cases published but they were unfortunately in the foreign literature and in languages that I was unable to certainly even have a clue at. And as a consequence unable to really get the parent papers that these data came from in many cases. 420 milligrams caused some lethargy and combative behavior. Again I wouldn't think that seizure activity is a real common thing with Buspirone and I wouldn't anticipate it to be very common with Gepirone. 250 milligrams was taken with Diazepam and there weren't any adverse side effects noted on that. How do we treat this overdose. Let's take a look.

My favorite no harm supportive care. My staff in Pittsburgh are saying what is he going to say? A glass of milk? Maybe all of these can be treated with a glass of milk and reassurance. Perhaps charcoal would be efficacious in these overdoses. I don't think cardiovascular toxicity is something we need to be terribly concerned about. CNS depression is not something we need to be overly concerned about. I don't think that in an

overdose this drug would manifest itself with a profile that would surprise us. We might see drowsiness or dizziness or nausea, headaches, vomiting, things like that but I don't think we'd see profound seizures and sequela that would make management of a patient like this very difficult. Next slide.

Let's turn our attention back to the EXETINES here. It's similar to Fluoxetine but it is very different. It's a third generation antidepressant. It's been in study for quite a while. There is a lot of chatter. If you go to Google you can find tremendous Internet chatter on this compound. People are dismayed it has been turned down. It was turned down through at least one phase or perhaps in the final phase of investigation at this particular point it's still not a drug that it's available as a prescription drug. It's a nice alternative to an SSRI. While it sounds like Fluoxetine, it's not. It's different. Pharmaceutical firms are striving to make safe, more effective drugs with few -- a lower and more gentle side effect profile and this appears to be a distinct advantage to this drug in addition to its very positive effects on major depression.

You can see the typical doses are in the range of 8 to 12 milligrams B.I.D. dosing based on the kinetics of the drug is preferable. Next slide, please. So from the mechanism standpoint as I mentioned to you earlier, it's similar, similar, to Fluoxetine structurally but it's mixture of two compounds. It's actually two compounds in one that are together called a selective norepinephrine inhibitor. Its primary mechanism of is to block -- it's a reuptake inhibitor. That's its primary focus of pharmacology activity. Other receptors and other actions that make some of these drugs troublesome like some of the other receptors. It

has only minimal effects on those. We probably are not going to see a lot of different side effects that you might characterize as being anti-must car inI can and Histaminic. It's pretty clean in terms of its mechanism of action. Next slide. Well, this is one that seems to work just a little bit more rapidly. You can see Gepirone was three to six weeks in terms of the activity. Maybe three weeks for antidepressant activity. Here is one that appears to be effective at least minimally in the first couple of weeks of therapy. When you do ingest it the peak levels occur fairly rapidly. That doesn't correlate with therapeutic effects but it certainly has the potential for correlate perhaps with toxicology effects we might see.

I want to remind you. When we get one of these overdoses it doesn't do any good at all to call the lab and we need a Reboxetine. How do people know if they took this overdose? Other than that it has nothing more than academic interest at this point in time. There isn't any reason that it will direct our therapy so I wouldn't waste your time, money and effort on that. I would spend the time, money and effort more on basic management of the poison patient. Next slide, please. Now, as with the other ones, it's absorbed fairly extensively. This one more so than others. It's distribution in quite low, is than it, compared to some of the others that have tremendous volumes of distribution. This more closely approximates the body water.

As you can see it is also very extensively bound up by proteins so that there will be very little free drug that is available. This is interesting. Unlike Duloxetine which is metabolized, this one is metabolized by 3A4. It doesn't have a lot of the same effects in

terms of inhibiting 2D6, for example, that Duloxetine does. You don't have to worry about that. There is no indication, at least that I was able to find, that this drug is an auto inducer, that will induce its own metabolism or effect the metabolism of other substances. On the other hand, conversely, if there is a drug that's also metabolized by 3A4, a drug that inhibits 3A4, if it's inhibiting 3A4 then the serum concentrations of -- I don't know what that means. I don't know if the therapeutic level is three, four or ten times normal if it has toxicology implications and as this is invested more and time will tell. Next slide, please.

What about the adverse effects? Well, there is very little information available. Here is one that will humor those of you sitting here and have persisted with us now for an hour and 12 minutes. The only case report I could find involving this particular substance was a male who experienced random spontaneous ejaculation two to three times a day. For those of you who needed a change of pace, there is a change of pace for you. That's the only case report I could find on this particular substance. An overdose, I don't know, you might be dealing with sort of the erotic patient perhaps.

But more likely not the case. The symptoms are minor things that may be would be of consequence, dry mouth, constipation, headache is common with these people. There were no effects on cardiac. It has a fairly safe profile when it comes to cardiac conduction. We've suffered through the horrors of some of the first generation antidepressants and all of the cardiovascular effects they've caused. This is a selective reuptake inhibitor. Maybe we'll see hypertension. I don't know how profound it might be. We might see the tachyarrhythmia. Seizures are theoretical because of the mechanism of

action. I didn't see evidence in human data. It was interesting to see the animal data where animals that were given 400 milligrams per kilo of this particular drug, that would be about 200 times or 500 times, I guess, the therapeutic dose of roughly eight milligrams. 400 milligrams per kilo in animals caused seizure activity in 20 minutes. If you see a massive overdose you might keep that in the back of your head and advise the caregiver that seizure precautions should be taken but that's a pretty massive overdose. Time will tell us whether or not this is going to be a problem. Next slide, please.

In terms of management of the overdose, again looking at I don't remember where I found this, it was Poisindex and Drugdex, if there was survival in 220 milligrams is the best I can do for you, that's about it. So I would accept maybe some type of effects that do no harm, good supportive care, activated charcoal if you think it's necessary if you get to people early on. I don't think the cardiovascular toxicity is very likely with this particular compound. Keep your eyes open for it in larger doses but I wouldn't anticipate it to be a life threatening events that we might expect to see. We're winding down here. We have one more antidepressant to talk about. That one is Viloxazine.

It's an interesting compound in that it's been around for about 30 years and I must say honestly it's the only one I heard of prior to getting this assignment from Jean to work with you in this particular project. It has been around for a long time and been used in Europe and it's -- next slide. One of those second generation-type antidepressants. As you can see from the structure on the previous slide it's a bicyclic type agent. It was for the treatment of narcolepsy. It was withdrawn for those particular purposes and then it was

used as more just an antidepressant, anti-anxiety agent with also some application in treating nocturnal enuresis. It was promoted abroad as being a good alternative to some of the other drugs that are available especially in the elderly. The daily dose as you can see sort of like taking a tricyclic antidepressant. It could be anywhere from 50 to 150 milligrams three times a day to exert it's pharmacology effects. This is an interesting compound as well. It is an Adrenergic agonist. It has amphetamine properties without the liabilities. It's set to inhibit norepinephrine uptake. It is not too different from Reboxetine. Next slide.

Well, there is a little bit known about the pharmacokinetics. You can see the distribution is low. .07 to .08. The metabolites are inactive and I didn't see that it would be any effect to induce metabolism or inhibit it at all. The half-life of this is fairly short. As you recall from the previous slide I discussed, that it was B.I.D. dosing it has a half-life of two to four hours. It means it is administered multiple times during the day to maintain its efficacy. What are the adverse effects? These are pretty well profiled and probably not a reason for me to go into any great detail on these because you can look at them on the slide yourself and go to a number of resources and find them.

I think the most important thing is to remember are that the cardiovascular incidence is low. I don't think you'll have to worry about cardiovascular toxicity. It doesn't appear to be profound. The one thing that did jump out at me and I've indicated it on the slide is that headache appears to be quite common in people who have been taking this compound. I don't know if this would translate to the overdose-type situation or not. Again, with a lot of

these drugs that affect various aspects of the nervous system, people have episodes of nausea and vomiting and this drug is not exempt from that by any means. This is the only one -- next slide, please, where there was actually information. I can actually find some cases to talk to you about and give you more than my guesses, hunches and what I gleaned from the literature. Well, as I said, Viloxazine has been around for a long time. You can see the first paper from 1976. We have a paper of almost 30 years ago published on this. Described 12 overdoses, people took anywhere from a gram to 6 1/2 grams. Remember the therapeutic dose is 150 to 450 milligrams a day. Put that in perspective.

Age range was pretty spread out from 15 to 44. Seven of them ingested co-ingested, them in combination with Viloxazine. Probably it's because these were combined with overdoses combined with -- it was very impressive that in all the scenarios I did read that there were no events that chronicled any cardiovascular toxicity. That's good. If this drug ever does make its way to the American market it's available in Canada and certainly in Europe, we don't have to worry about that. And then there was another interesting paper if you read this as a SPY and said I have a Viloxazine overdose, do a quick literature source and obtain this paper. It's in our files in the Poison Center done by Buckley in 1998.

If you read through that it basically says this is a pretty toxic drug. Step back you see I think we better be very aggressive with the management of this one because he said it's the third highest fatality index. That shouldn't surprise any of us that December ip ra

mean -- they calculated a fatality index and first of all this drug wasn't used a lot. There were very few prescriptions. It had several thousand prescriptions and one death. This gave that drug the appearance of being associated with a very high index of lethal and high mortality index when I think it's a misinterpretation of the literature to come away with that conclusion based on everything else I've seen. I don't think if you get one of these overdoses you should be thinking about this as oh my gosh the worst overdose we've ever seen coming up here because it's ranked third in the fatal toxicity index by the Buckley paper. I would basically dismiss that aspect of it. The other data seem to be accurate but that I would certainly dismiss. The next slide, please.

Now, managing overdose. We know from previous slides that people have survived 6 1/2 grams. It should help you when you write down some of these things, here is at least a standard. I would go to the paper. It's not comprehensive. It's a series of case reports, a very good paper. If you have get it from your library I think it would be very good. Again the other admonitions that I've shared with you over the last yearly hour and a half about good supportive care, activated charcoal certainly should prevail plus milk and reassurance. I don't think the cardiac vascular toxicity is likely. That concludes my formal remarks.

I would like to take this opportunity to thanks Maxine Jones and HRSA for sponsoring this and providing the grant to make this happen and hopefully there will be a lot more webcasts to educate our spies. It's valuable and an important mission to make sure that there is good contemporary education of our spies. They are the foundation of our Poison

Centers and without them we wouldn't be anywhere. Keep up the hard work and thank you for your help. I would also like to thank Jean and the whole spy committee, Peg for coordinating here today and everyone for listening in and participating. Taking your lunch hour, breakfast hour, the extra time that you took to spend with us. So without any more I would like to turn it back over to Peg and we would be happy to try to answer questions. Let's see if I can field any of these questions that you might have. Thank you again for your kind attention.

PEG CAMPBELL: We do have a few questions from the Blue Ridge Poison Center. Scott and I realize in watching the first broadcast that one person usually signs in so you might get several questions coming from a Poison Center and it looks like a same person. In this case I know Scott, probably all those questions are from him so we'll start off with the first one. He is asking he says hello. Does the F.D.A. post side effects from animal studies?

EDWARD KRENZELOK: Hi, Scott, it's been a long time since I've seen you. Thank you for your question. It's a good question. I don't know the answer to that. I suspect that in some of their data since animal data are the foundation of a lot of the preliminary phases that that might be the case but I don't know the answer to it. An excellent question and one that I'll need to research when I get home. Thank you for bringing that to our attention. Certainly there was a lot of animal data available on all of these particular topics

that I saw but it didn't include animal data because some of it with a pretty far out. How many kilos in a duck I didn't think applied.

PEG CAMPBELL: Have we lost contact here with -- I'm not sure if they're hearing us. Still live, OK. The next question from Scott was about Exenatide. Could we assume ingestion would be non-toxic?

EDWARD KRENZELOK: Given this is a peptide compound like glucagon. I don't think it would produce toxicity based on the fact it's an amino acid and would be destroyed in the G.I. tract.

PEG CAMPBELL: Also from Scott Wylie, would--

EDWARD KRENZELOK: They oretically a trio tide might be beneficial, but I think my guess is with Exenatide we probably aren't going to see profound effects that we might see with insulin or an oral hypoglycemic agent. Seemingly it would be useful.

PEG CAMPBELL: I had wondered, actually, if there would be an abuse potential since it goes down the G.I. tract and makes people feel full.

EDWARD KRENZELOK: That's a good question. I hadn't thought about that myself. I was looking at things about toxicology but that's a great question. Anything is possible. Take a look at the people who use Ipecac and a variety of means as anorexic you --

bulimic components of the disease, it might be one of those things that people would do. My guess is it would be expensive and difficult to obtain, but certainly like anything else, abuse is certainly possible, yes. Good question.

PEG CAMPBELL: Scott Wylie had another question about the Viloxazine and no abuse potential.

EDWARD KRENZELOK: While it had sort of the stimulant effects in terms of -- remember, amphetamines stimulate the release of them, it might be stimulating the release of these things in a more moderate fashion and therefore you don't see probably the significant highs that you might see with other amphetamines and maybe that's the reason. I didn't really see anything, nor -- I feel comfortable not to talk any more about it. That's my off the cuff thought on it.

PEG CAMPBELL: Kimberly WITT wrote a question from Florida Poison Center in Tampa. Can you mix the Exenatide with insulin in the same syringe?

EDWARD KRENZELOK: My guess is that you wouldn't for the following reason. If you had to resort to insulin, you probably would not use Exenatide. Exenatide is really being developed to augment oral hypoglycemics so it's there to help the oral hypoglycemics and be synergistic with them. If you had beta cell failure the Exenatide probably wouldn't have any benefit because you would be resorting to the use of insulin at that point in time. My guess is that the two would not be used together for that particular reason.

PEG CAMPBELL: We have a question. I'm not sure where this woman is from. It says this is Emily green. I guess she was typing her name in. Wanted to know if Viloxazine has an amphetamine-like effect and if it does why is it not used as an anxiety med and why wasn't it approved?

EDWARD KRENZELOK: I must plead ignorance. The therapeutic end is something I'm not very familiar with. One of the shortcomings I tried to focus on more the adverse events. Great question. I don't know but I can try to find the answer for you.

PEG CAMPBELL: Susan Anderson, a nurse from Poison Center in Wisconsin. She's asking if there is any information or recommendation for ingestion in therapeutic error or overdose for pregnant women -- let's see -- didn't say.

EDWARD KRENZELOK: The one thing I can tell you I couldn't find any significant pregnancy information on any of these. Duloxetine was just approved and I neglected to look at the pregnancy information which I could do very quickly as we're going to the next question. But I know that pregnancy information was very difficult to come by. I specifically tried to find information. In the last webcast a number of you asked Wayne questions about pregnancy. My guess is that none of these are probably approved for and during pregnancy. My guess would be the Exenatide would probably be a relatively safe compound to use -- to give, given its structure and nature and so on. I don't know about the other compounds.

PEG CAMPBELL: Kerri palmer was rocky mountain had a question. Would you see an increase in glucose and hyperglycemia?

EDWARD KRENZELOK: You might see an increase in the hyperglycemic patient but again in the normal glycemic patient. The patient without diabetes, everything I am led to believe is that you would not see an increase in glucose. If we had a healthy person you probably wouldn't see an aberration in that person's glucose level. The glucose is being metabolized in other pathways and you aren't going to see an increase in glucose. You might have a slight bump in the glucose in a diabetic patient. But probably not profound.

PEG CAMPBELL: Kimberly has a question. From the Tampa Poison Center. What is the dose range for Exenatide.

EDWARD KRENZELOK: It was five micrograms B.I.D. for 30 days. Then after that it was 5 to 10 milligrams a day twice a day. You start out at 5 micrograms twice a day and then you basically go up to 10 micrograms twice a day. So that appears to be the ongoing therapeutic regimen that people are using right now in the studies.

PEG CAMPBELL: We don't have any questions right now. Can you think of anything else you would like to comment on?

EDWARD KRENZELOK: A couple of other things. Spies, thank you for your hard work. Remember we have these challenging questions you're not the only people challenged

with these. I was very challenged by these particular topics and putting them together and equally challenged by your questions. Thank you very much for the opportunity to participate. Thanks to the folks in Chicago who seem to have done this webcast flawlessly and thanks again to everyone here. It was a fun experience and appreciate the opportunity to be here today with you.

PEG CAMPBELL: I would also like to again thank HRSA and Maxine Jones for making this available to us. I hope we'll have many more webcasts in the future and appreciate and see if there is any other questions here. I'm not sure -- you know where Kay is from?

EDWARD KRENZELOK: Elk River, Minnesota. It's my sister. Thanks, Kay.

PEG CAMPBELL: That's great. Any other sisters out there?

EDWARD KRENZELOK: Old girlfriends? No, better not bring that up.

PEG CAMPBELL: OK. We have a little bit more time here, don't we? So if there is -- looks like it was -- like to ask any more questions. It's very informative. I agree the Exenatide, 30% causing nausea I would think that would eliminate a lot of people taking it.

EDWARD KRENZELOK: I think it will be a roadblock in the use of that particular product. Also it seems like that people do develop tolerance to it with more long term use. Probably getting over that initial hurdle of the nausea may be difficult for folks and I

suspect that Poison Centers may get calls from people who inject this and then develop nausea and call the Poison Center for help. Remember, it's a therapeutic sort of side effect and don't be surprised if it does occur.

PEG CAMPBELL: Wally asked are there any plants for an implant or other delivery means since it's injectible?

EDWARD KRENZELOK: Good question, I don't know. I didn't look into it much further than that. I suppose that is somewhere down the line after it gets approved.

PEG CAMPBELL: Rita submitted a question. Should we use whole milk or 2% with that reassurance?

EDWARD KRENZELOK: I told you if I brought out the glass of milk and a little reassurance my staff would jump all over this. Thank you, Rita, that's a challenging question. I would say super skim would be the best because it's best for everyone's diet. We're rapidly going down the hill here.

PEG CAMPBELL: Yes. Maybe you have some brothers.

EDWARD KRENZELOK: I didn't tell him about this.

PEG CAMPBELL: The drugs at the F.D.A. site and I wonder how many Poison Centers have -- they all have their own websites. We have one we use internal to the Poison Center that we can bring up information in front of us and we'll put up our favorite contacts and so forth that we can access.

EDWARD KRENZELOK: We do as well. We have an Internet site like that. It would be a good thing to have these links built in. Drugs at the FDA. Have your favorite avenue to Medline built in to get around some of the hurdles to exit out and get into Internet explorer and the things that take time when someone is calling the Poison Center. A good idea. Everybody building the Internet sites and relying on them.

PEG CAMPBELL: It helps. I've noticed recently that the Internet is such a vast resource that many things now that don't necessarily come up on Poisindex I will be able to find by just going to a search engine.

EDWARD KRENZELOK: Exactly. And again we always have that admonition, there is a tremendous amount of give and take back and forth on a lot of these drugs. If you want to see interesting information from a variety of IRATE people go to the Reboxetine/Google hits and indicated their displeasure for the FDA not recommending Reboxetine. They say it's the best thing since sliced bread for their mental health. That can be very helpful as well.

PEG CAMPBELL: Any other questions out there? I think we--

EDWARD KRENZELOK: You know what it's like to be Regis and Kathy Lee, right? You have to keep coming up with this chitchat. Other topics in toxicology you would like us to talk about? We can tell stories about some of those.

PEG CAMPBELL: It is also nice looking forward to the annual meetings, the opportunity to get together with other spies and discuss how different centers deal with different issues.

EDWARD KRENZELOK: I want to encourage everybody if you can and on the list to come the North American Congress of clinical toxicology September 9-15 in Seattle. I know the spy committee has excellent programming. Maxine and HRSA will be there helping everyone work through a lot of the issues that involve Poison Centers today with regard to funding. The meeting symposia are outstanding. There is a tremendous number of meeting symposia. If you want to hear a debate on Ipecac you better come. There will be a debate between two people. I'm one of them.

The other is Dan COBAU looking at the pros and cons of Ipecac and examining the position statements, the guidelines out there and that will be kind of a fun and I'm sure spirited debate. Hopefully trying to resolve some of the controversy. We all still seem to have controversy about Ipecac, charcoal and the things basic to the management of the poison patient. Not only that but a number of other outstanding symposia. Don't forget, stay until the end. There is a full programming through Tuesday and there is a great president's reception, I might tell you, that the president's reception will involve after the

dinner sort of a mystery murder and it will be a number of people from the organization that will be partaking and maybe you can figure out, you know, who killed whom with the candlestick in what room. But this is put on by a professional organization and it has every, every indication that it is going to be a fun event involving people that are near and dear to many of you in Poison Centers. Come out and enjoy the North American Congress. It will be a great meeting and the host city Seattle is wonderful. The hotel is right downtown, five blocks from the big market. There are all kinds -- a Starbucks on every corner, of course, in Seattle. There are a number of things to do. Wonderful restaurants. If you're stranded in Chicago last year and I could only get to McDonalds, just walk out the door of the Sheraton and you'll be within feet of dozens of restaurants.

A wonderful venue for you this year and very inexpensive as well in terms of the dining opportunities. It will be a great meeting to attend academically, socially and even financially. Well, Maxine, what do you think? Our sponsor says that we're going to say goodbye. Regis and Kelly, I guess. Until we meet again tomorrow morning.

PEG CAMPBELL: Until we meet again tomorrow morning.

PEG CAMPBELL:: Thank you very much for tuning in today.

EDWARD KRENZELOK: Bye.