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Pain Managment in Polycystic Kidney Disease

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Dr. Torres

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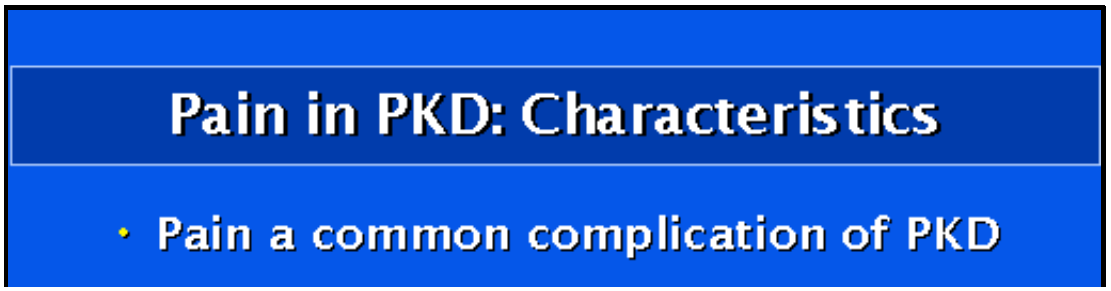

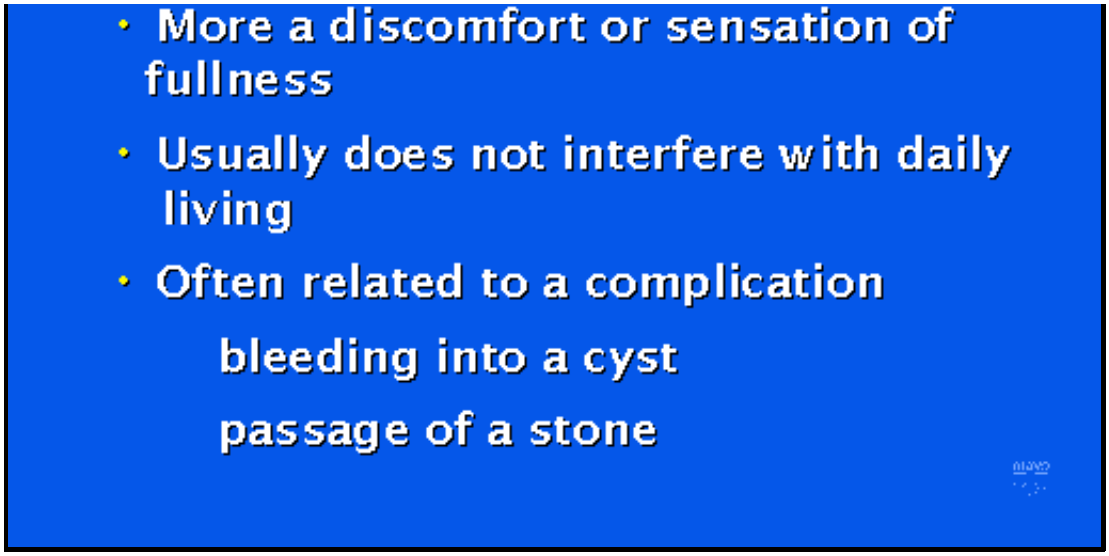

Pain in PKD
As many of you know, probably because that is the reason why you are here, pain is a very common complication of polycystic kidney disease or PKD. However, in most patients with PKD, the pain is not really a pain. It is kind of a discomfort with a sensation of fullness, some heaviness, which really does not interfere significantly with the quality of life. In some patients, the pain is related to a complication, like bleeding into a cyst or passage of a stone. But this pain, although it is severe, is a pain of limited duration.

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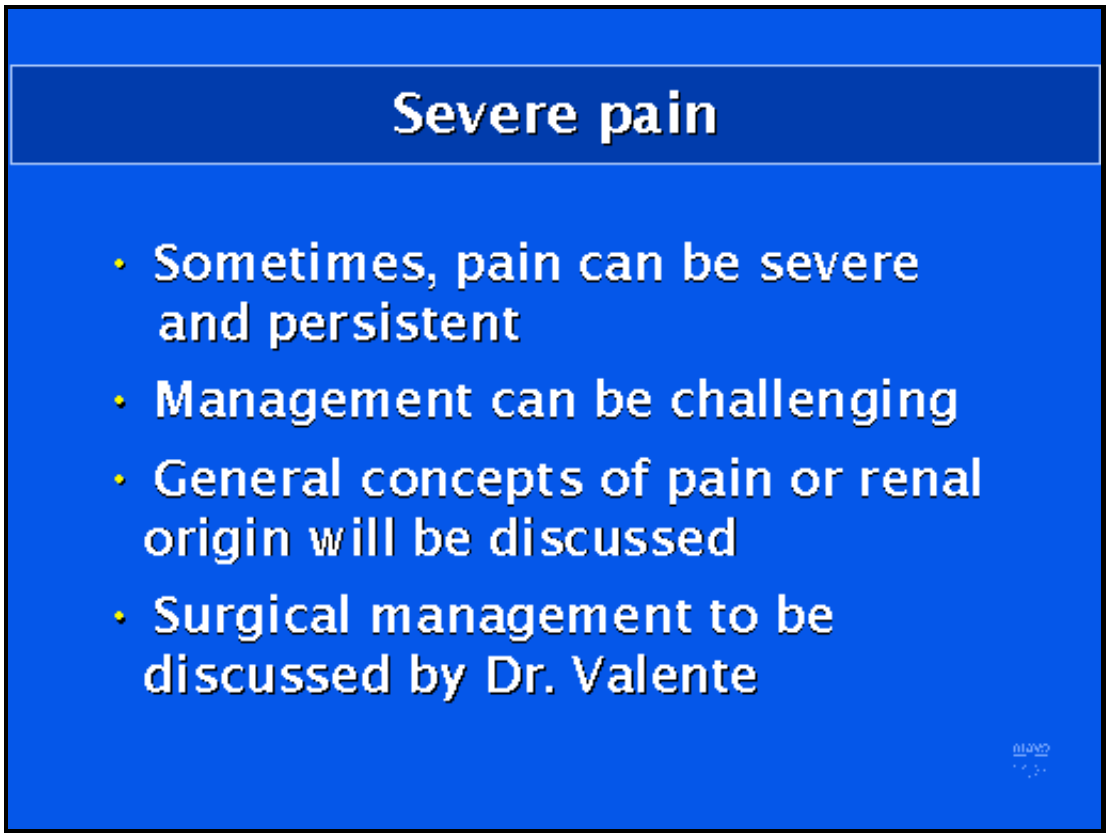

Severe pain
There are only a few patients with PKD in which the pain is not only severe but persistent. In these few patients with polycystic kidney disease in which the pain is severe and persistent, these can become very frustrating for the patient, very challenging for the physician. And it is precisely about this situation that this session is going to be centered on. So my discussion will be mainly related to this situation, and the same will be in the

case of Dr. Valente. What I will do... my part is the easy part. I will discuss some general concepts about pain, pain of renal origin and management of chronic pain. Then Dr. Valente will discuss in detail surgical options for the treatment of pain related to polycystic kidney disease with emphasis on some innovative, minimally invasive approaches in which he is currently working.

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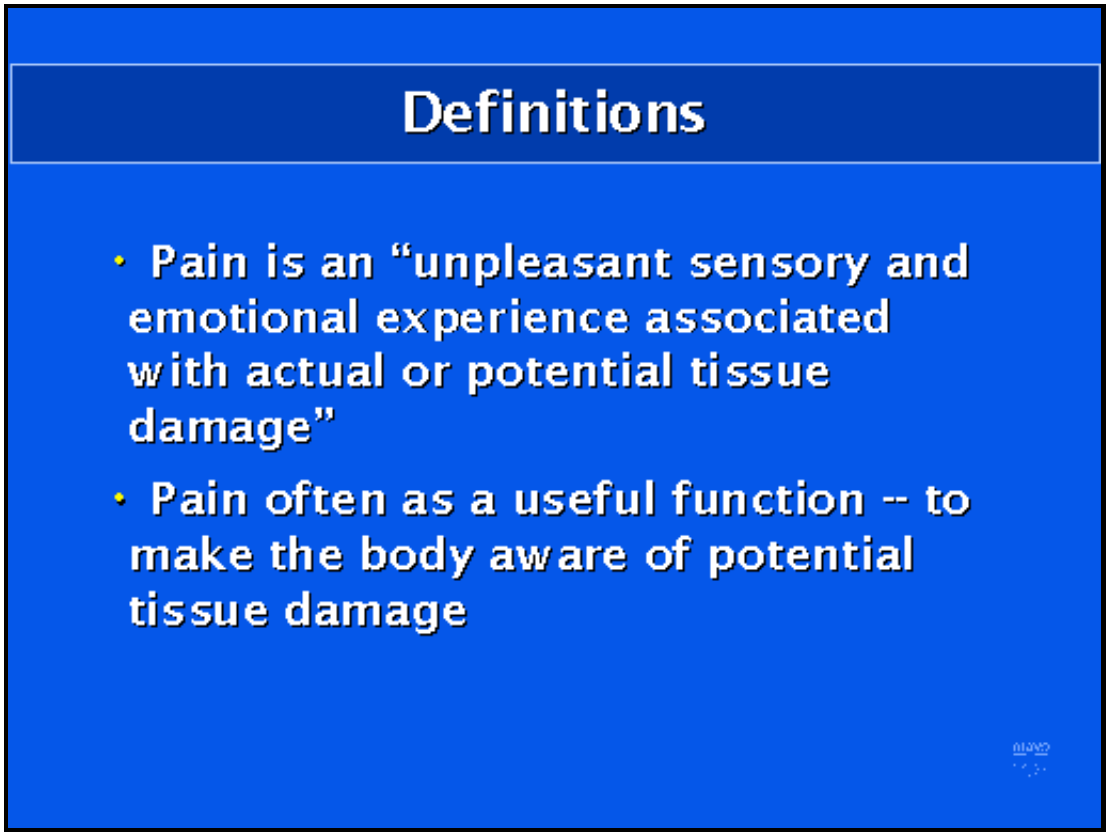

Definitions of pain and its potential usefulness
To start with, if I can have the first slide. All of you know what pain is. That is something that almost every human knows. Not every human, but almost every human knows. In the medical literature, pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.

Despite the unpleasantness of pain, pain is a useful function by which the brain becomes aware of some potential or actual damaging going on at the tissue level and therefore is capable to react appropriately. So despite the fact that pain is an unpleasant experience, it serves a very useful function which is important for the maintenance of health.

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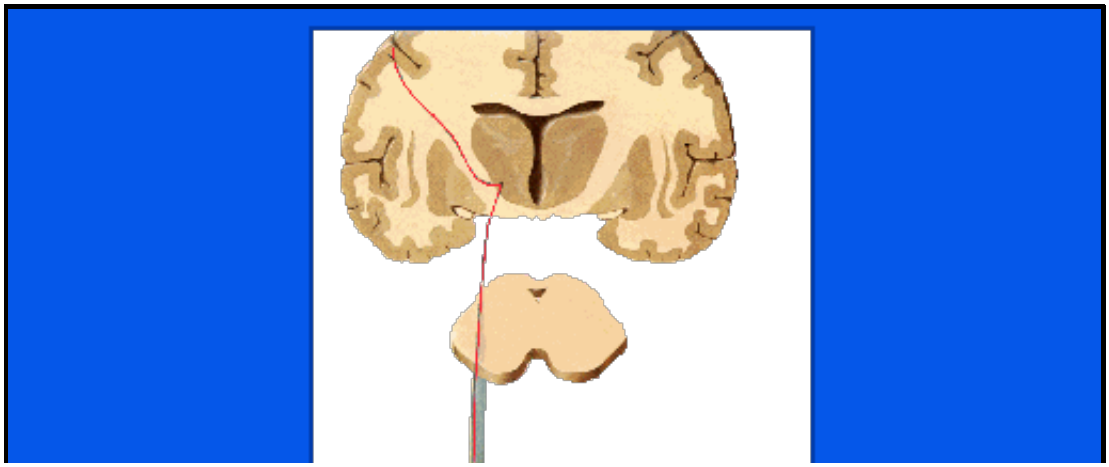

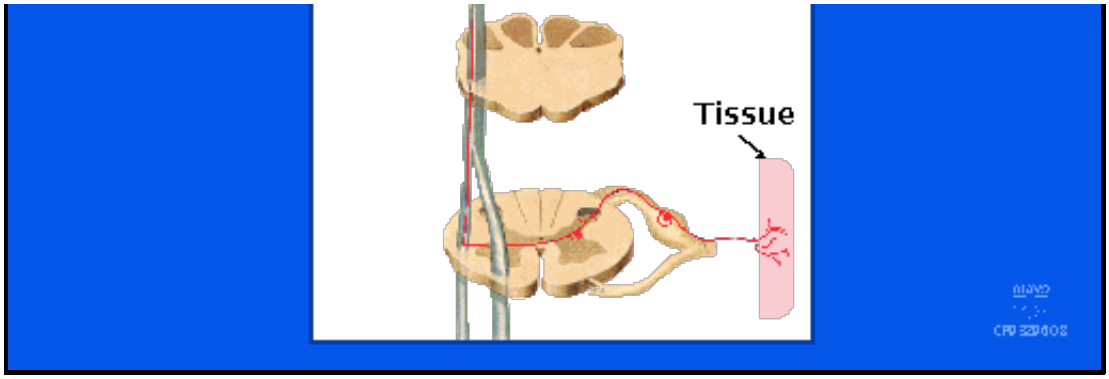

How pain is communicated to the brain
This function requires the integrity of thousands and thousands of chains of specialized nerve cells that can link to each other and communicate with the peripheral tissues with the brain, with stations or stops in the ganglion... and also ganglia in the spinal cord, in the brain stem, and in the brain.

Now the nerve endings of these more peripheral nerve cells in the tissues contain receptors which are capable to sense heat, mechanical stretch or pressure, and chemicals that can potentially cause tissue damage. These receptors are called nociceptors because the name for damage in Latin is nocere and the word comes from Latin. So these are called the nociceptors.

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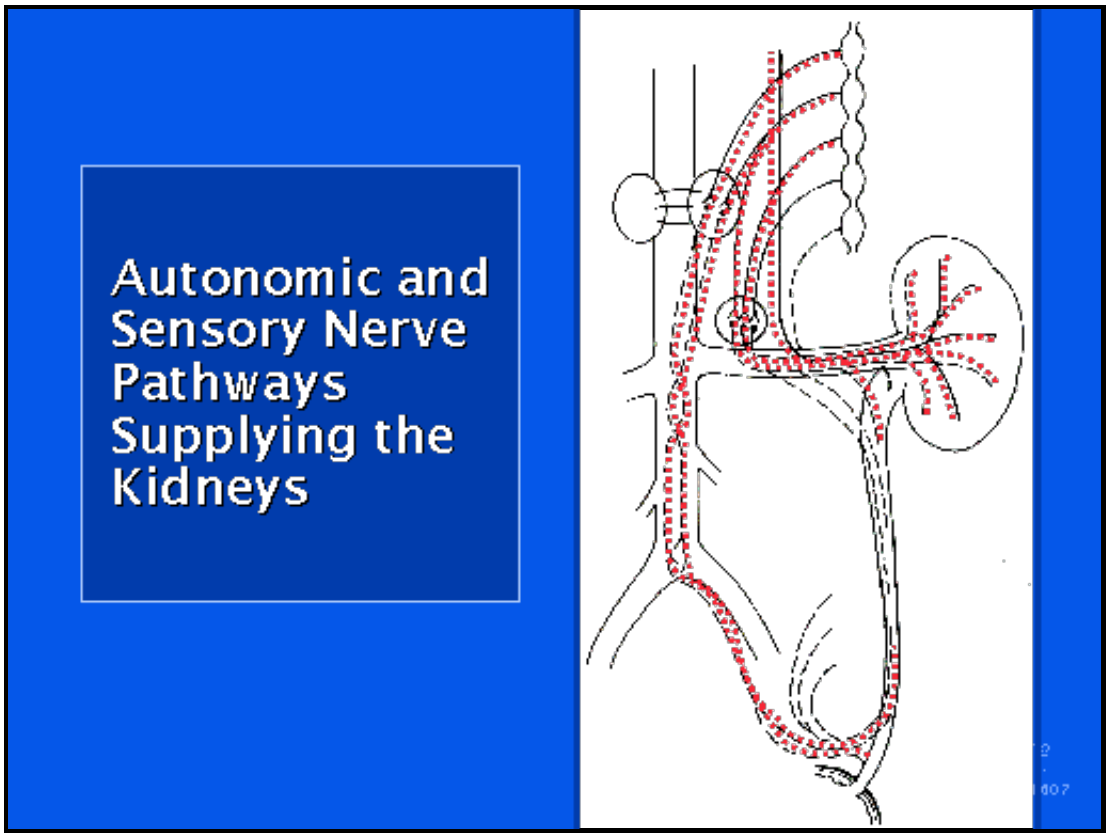

Pain pathways from the kidney to the brain
I don't see this slide very clearly, and I don't know whether you can see it better than I do, but this is to schematically show how the sensory nerve fibers that come from the kidney... how these travel eventually from the brain. And they travel around the blood vessels and from the blood vessels, follow different courses which can involve the aortical renal ganglion and the celiac ganglia and a number of nerves, including the lumbar nerve and the splenic nerves and the sympathetic chain at the levels of the dorsal, thoracic and upper lumbar levels.

So the migration of these pain signals from the kidney to the brain goes through a number of different pathways which are important. This anatomy will become important later when Dr. Valente talks about some different surgical procedures that can be performed to interrupt these pathways for pain transmission from the kidney to the brain.

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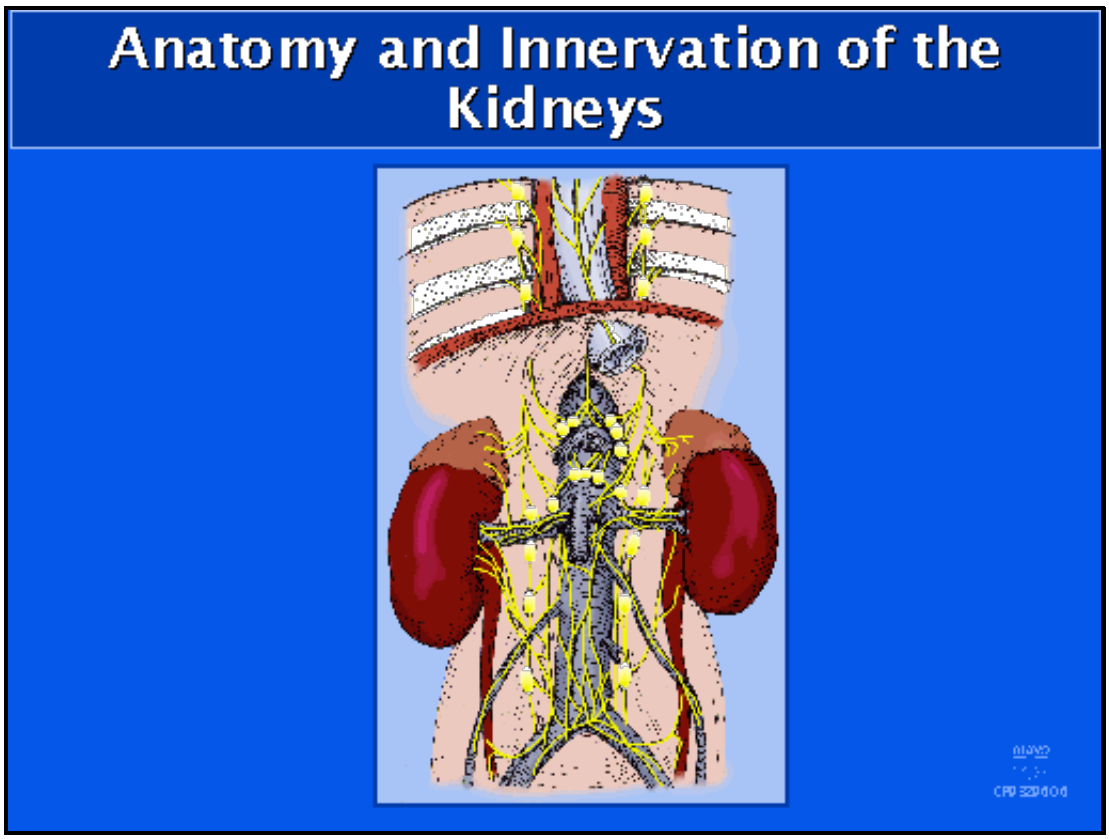

Neural anatomy of the kidneys
The following slide shows a more anatomically correct picture in which the nerves and nerve ganglia are illustrated in yellow and following you can see the blood vessels. You can see the distribution of the nerve is quite widespread and quite variable from patient to patient, which makes intervention to interrupt these pathways somewhat kind of delicate and specialized.

Role of pain receptors
Now you can think about these nerve fibers that transmit the pain or the sensation of pain from the peripheral tissues to the brain as electrical wires. But in reality, they are much more complex than electrical wires. The transmission of the sensation of pain from the peripheral tissues to the brain involves hundreds of chemical messengers and receptors and ion channels, which are all under some type of genetic control.

Every one of us has different types or different subtypes of these different molecules. What this determines is the fact that the sensitivity to pain is highly variable from patient to patient or from human to human and it does not have to do with bravery or macho feeling. It has to do with your genetic background. In a way, there are patients who are more susceptible to pain than other patients. That is very important also to understand the nature of chronic pain, and so we will go in a moment.

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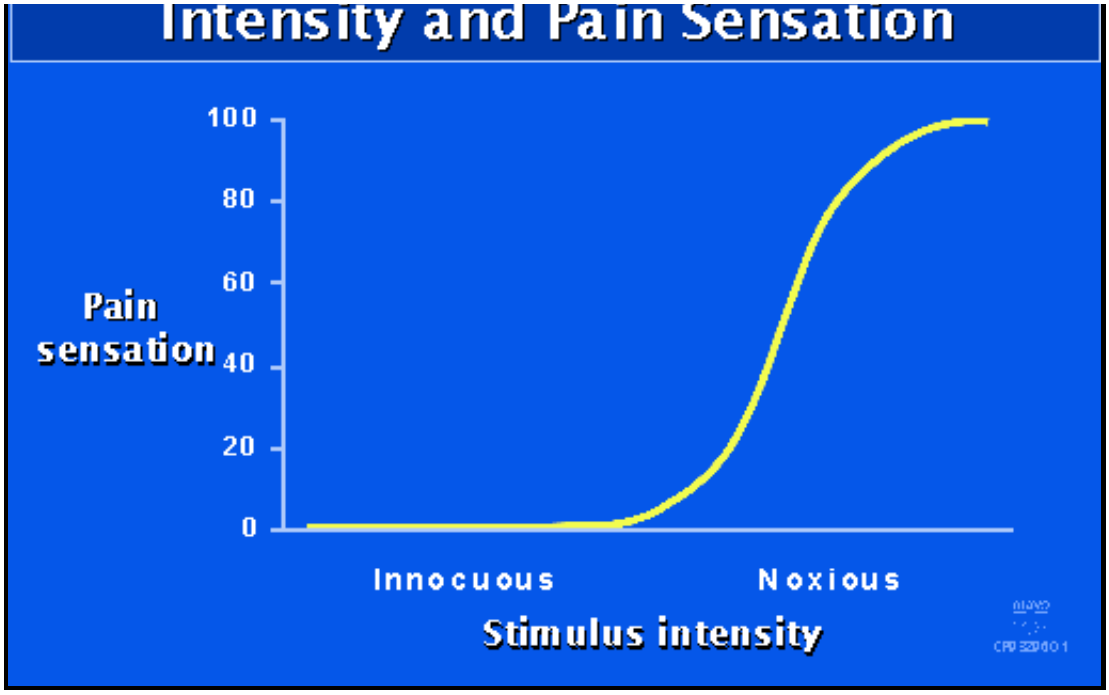

Pain sensitivity: the "S" curve
Now the relation between the intensity of the stimulus and the sensation of pain can be described by an S-shape curve with stimulus at the very innocuous level not causing kidney pain at all, and then as the stimulation goes up, causing more and more severe pain. Now this curve describes the threshold for the sensation of pain. If it is displaced to the left, it indicates much less intensity of stimulation will cause more severe pain. If it is displaced to the right, the reverse will occur.

So displacement to the left indicates more sensitivity to the pain; displacement to the right indicates less sensitivity to pain. And humans and animals are highly variable in what this threshold for pain is, with some subjects being more susceptible, some subjects being less susceptible. And some of this is determined genetically.

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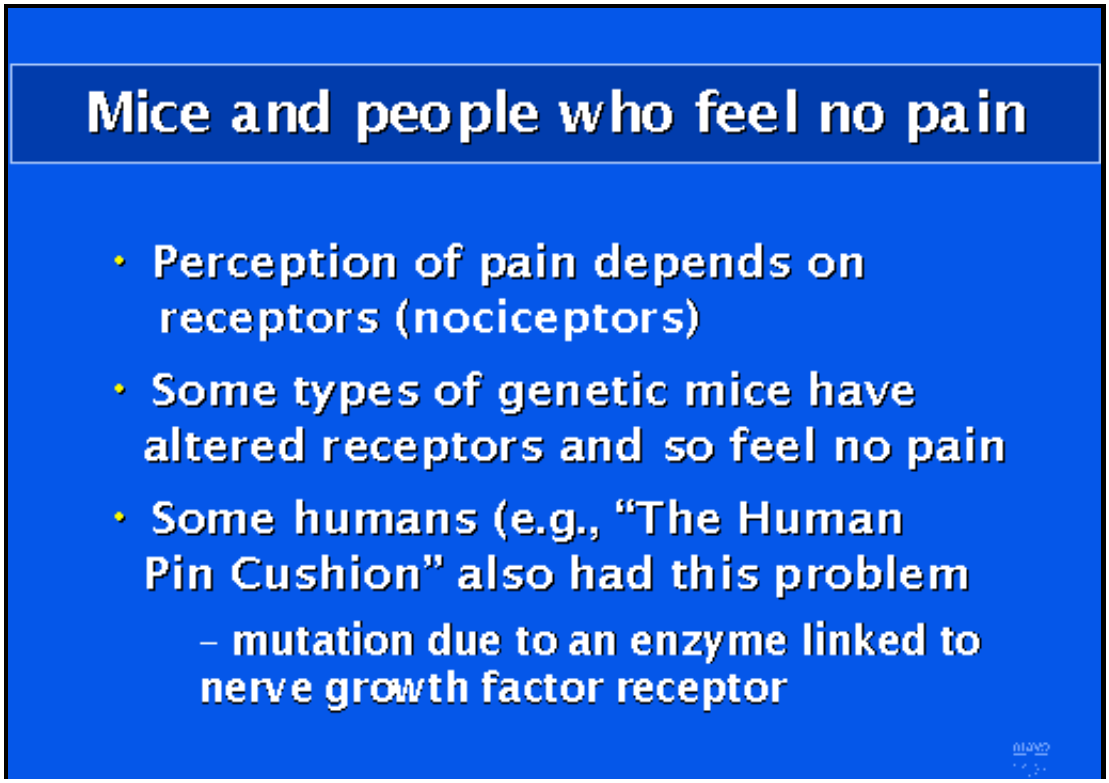

Individual responses to pain: genetic differences in pain receptors and enzymes that affect them
Now this is something that has become increasingly obvious now, and you can create mice with different types of genetic mice, in which they are completely resistant to pain because they lack some of the receptors which are important in the transmission of pain from peripheral tissues to the brain.

In humans, this can also happen. The best example for that is known as The Human Pin Cushion, who was a person who used to work in carnivals and circuses in which he could have all kinds of needles stuck into him because he had no sensation of pain whatsoever. And now we know this is due to a genetic lack or a mutation that inactivates an enzyme that is linked to a nerve growth factor receptor. This is just to indicate how the variability of sensitivity to pain has much to do with genetic factors and less to do with how brave really you are.

If you are interested in more about that, there is a very good review article that was published one year ago in the ***Proceedings of the National Academy of Science***, which is a very reputable journal, very high-quality journal. In this article, the genetic mediation of sensitivity to pain and sensitivity to inhibition of pain is clearly discussed.

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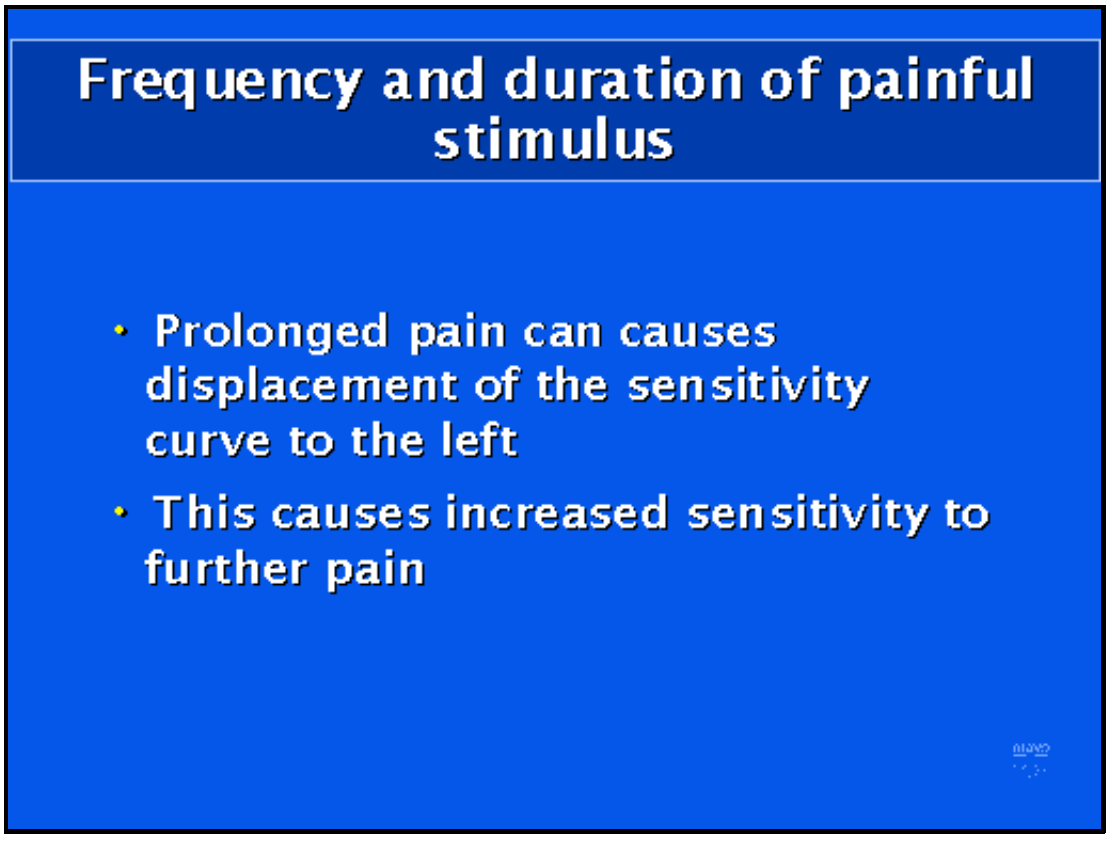

Prolonged pain can increase pain sensitivity
Another factor which is very important in determining this threshold for pain is the frequency and the duration of the stimulation. The more frequent the stimulation is and the more the duration of the stimulation, there is a displacement of this curve to the left. In other words, with more prolonged stimulation by pain producing a type of stimulation, there is increasing sensitivity to the feeling of pain. This is very important to understand the nature of chronic pain.

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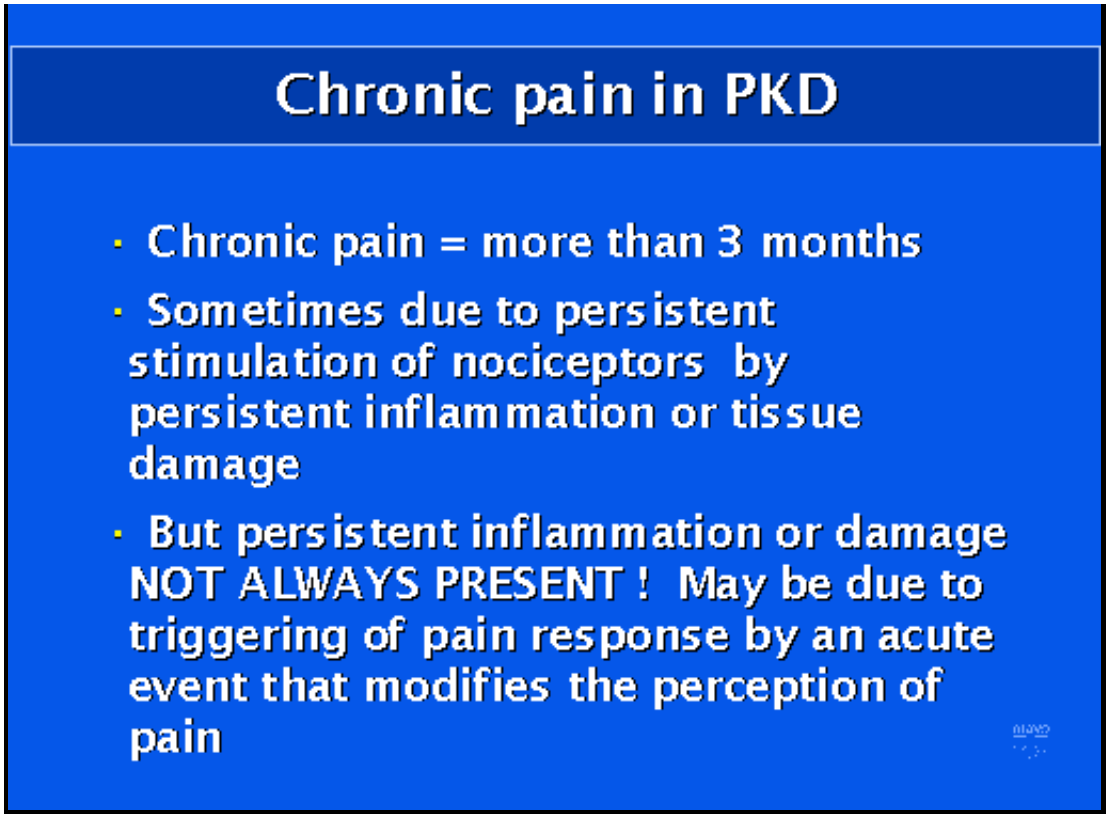

Chronic pain: persistence due to nervous system alterations

Chronic pain is arbitrarily defined by a pain that has lasted for at least three months. That is an arbitrary definition which is used in medical literature. This chronic pain may be due sometimes to persistent stimulation of the nociceptors by some inflammation or some tissue damage. But more frequently than not, this chronic pain is not due to the persistent stimulation of the pain receptors but is due to changes in the nociceptive processing within the nervous systems despite the fact that the acute event that triggered the pain has gone away. There has been a modification in the nervous system that results in the persistence of the pain. That is very important in chronic pain.

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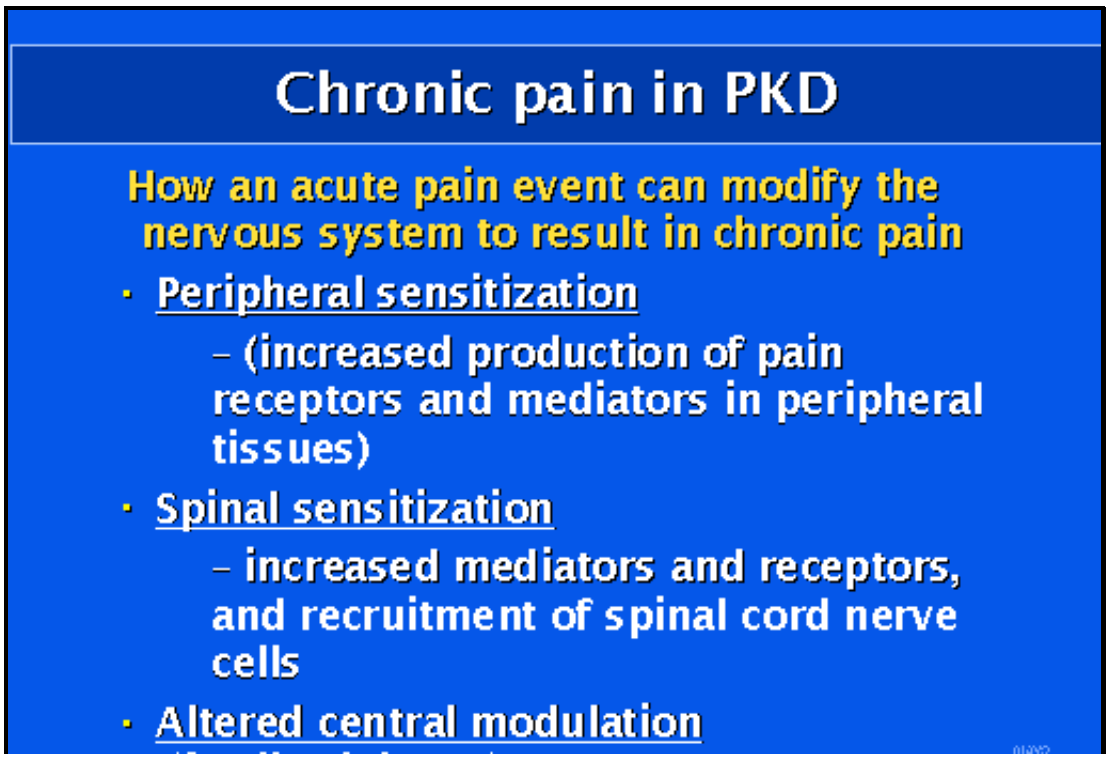

Three mechanisms of chronic pain persistence
In some words, in many cases of chronic pain, the chronic pain is not due to persistent inflammation of the tissue but is due to some disease process in the nervous system itself. This disease process is due basically to three phenomena.

One is called **peripheral sensitization**, which is due to the fact that in response to the pain, the nerve cells in the peripheral tissues increase the production of receptors and mediators of pain and also increase the activity of the receptors by becoming phosphorylated.

There is another mechanism, which is central **sensitization at the level of the spinal cord**, which is also due to the same mechanisms and also to recruitment of additional nerve cells.

And then there is another mechanism which is **ultracentral modulation**. When we have some type of painful response, there are some feedback loops that involve higher nervous system centers, which either can inhibit or potentiate a sensation of pain. With chronic stimulation, with chronic pain, what happens is you have a blunting of the inhibitory pathways and you have stimulation of the stimulatory pathways.

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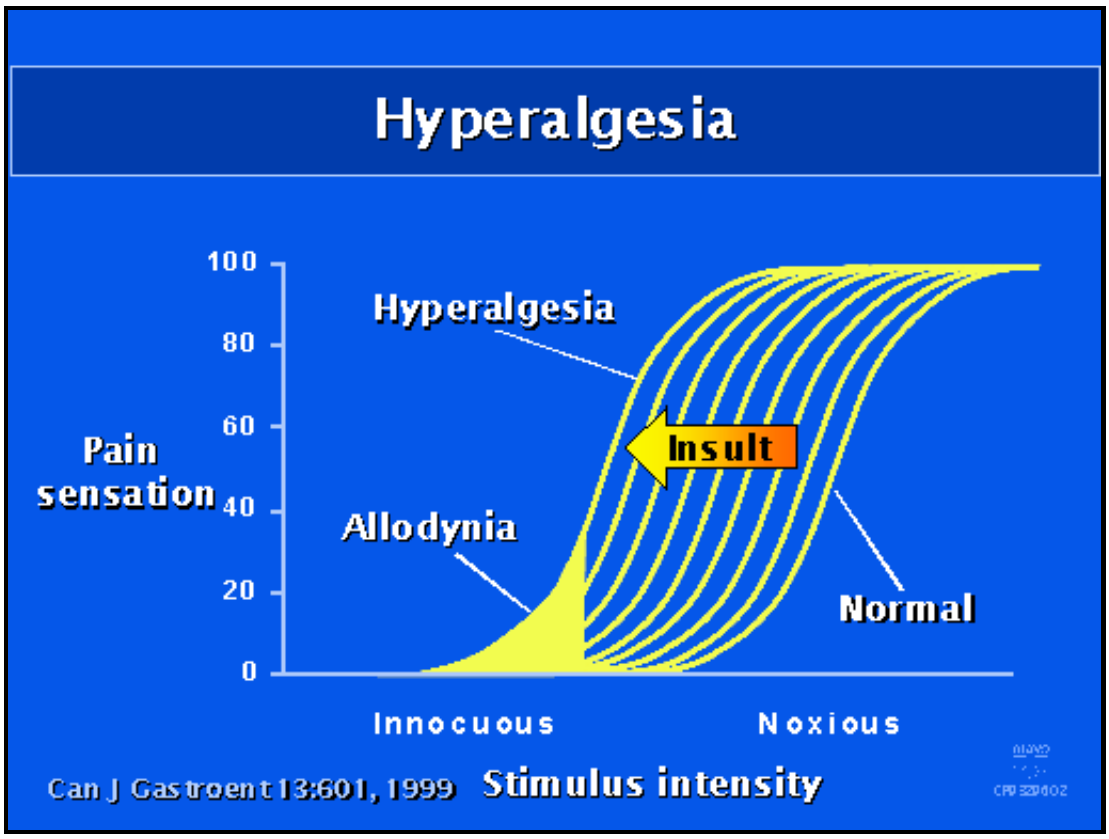

Shifting of the pain sensitivity curve to the left
All of these can result in is chronic pain. With persistence of the insult, there is a progressive shifting of the S-shaped curve towards the left. So there is increased sensitivity to pain. This results in the fact that a stimulus that normally produces only a little amount of pain, after chronic pain it then results in a significant amount of pain. This phenomenon is called hyperalgesia. Also what happens is that the stimulus that normally produces no pain, after a chronic injury, then it produces pain. This is a phenomenon that is called **allodynia.**

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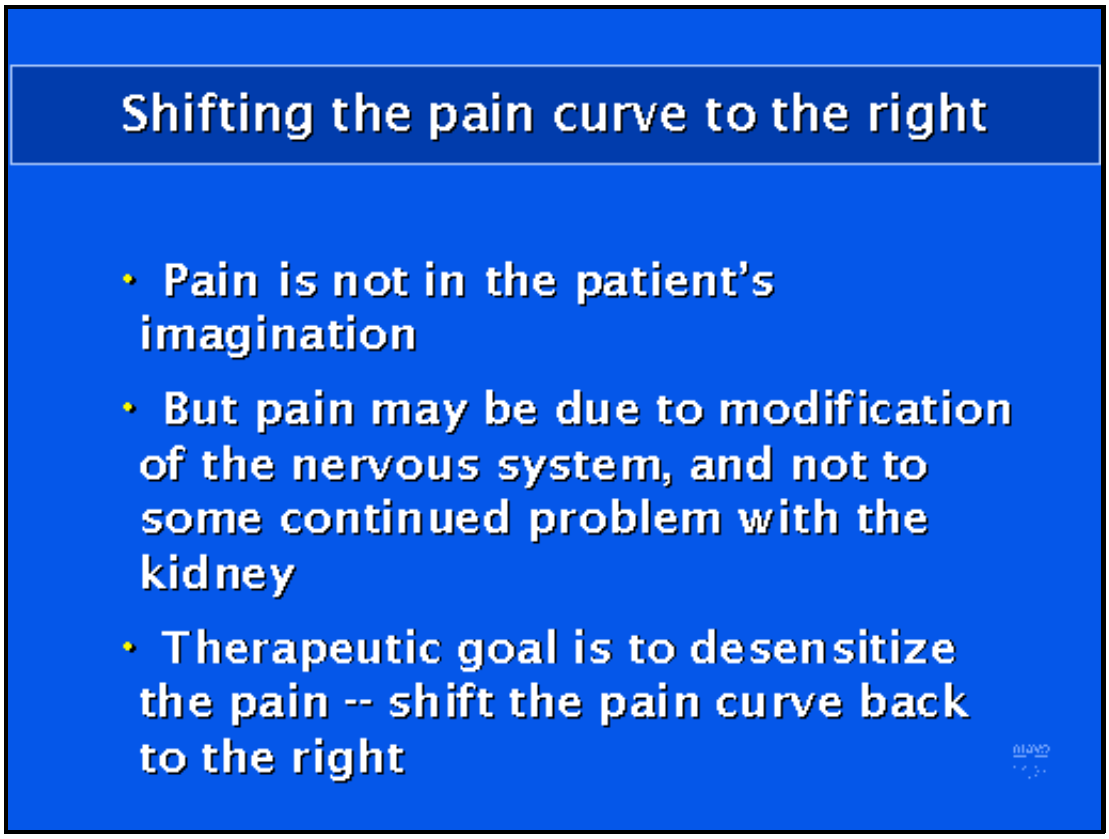

In the chronic management of pain what is very important is to try to reverse this pattern and to shift this curve back to the right. That is what we want to do with medical maneuvers that deal with treatment of chronic pain. It is very important for patients to understand that because sometimes it is very difficult for them to understand, for patients to understand that maybe the chronic pain is not due to persistent ... that something is wrong in the kidney. They do not understand that if the physician tells them that there is nothing wrong in the kidney but the pain is persistent, that is not saying that the pain is in your head. It is a very real phenomenon, and that is the explanation for this. What needs to be done is to understand that and try to reverse this pain curve to the right.

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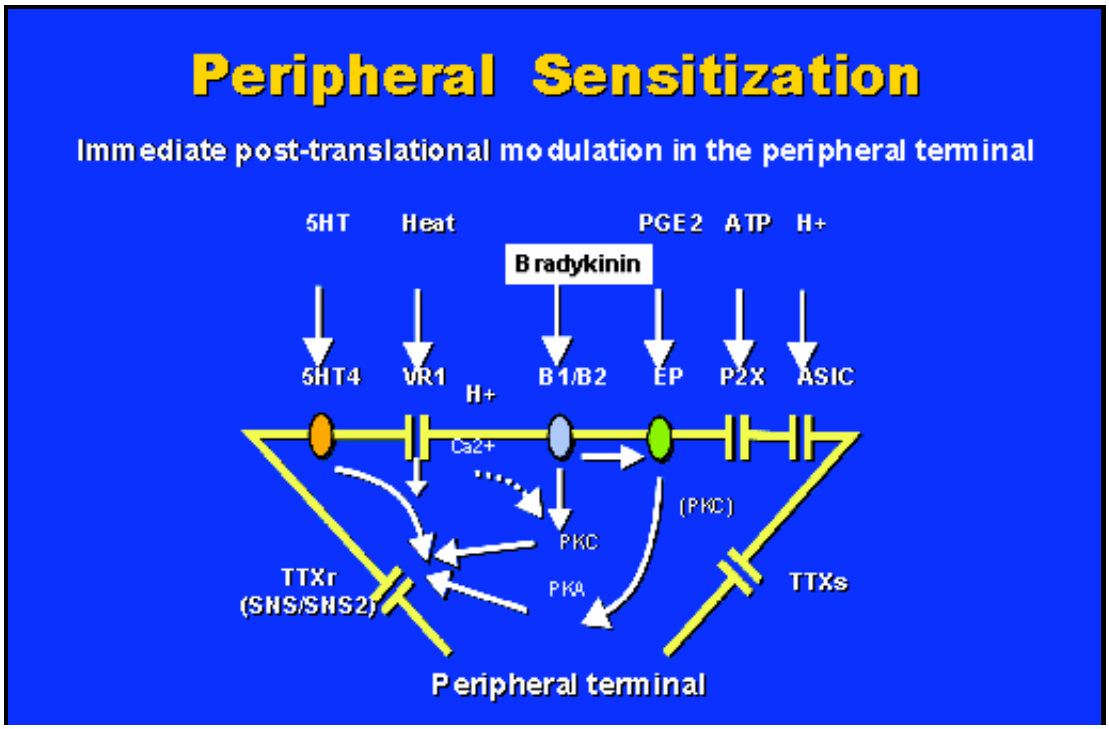

Source: Woolf CJ et al, Proc Natl Acad Sci U S A. 1999 Jul 6;96(14):7723-30. Review.

Peripheral sensitization in detail
The following three slides are just...not to discuss with you because they are very complicated slides, but just to give you the message that this phenomenon of peripheral sensitization,

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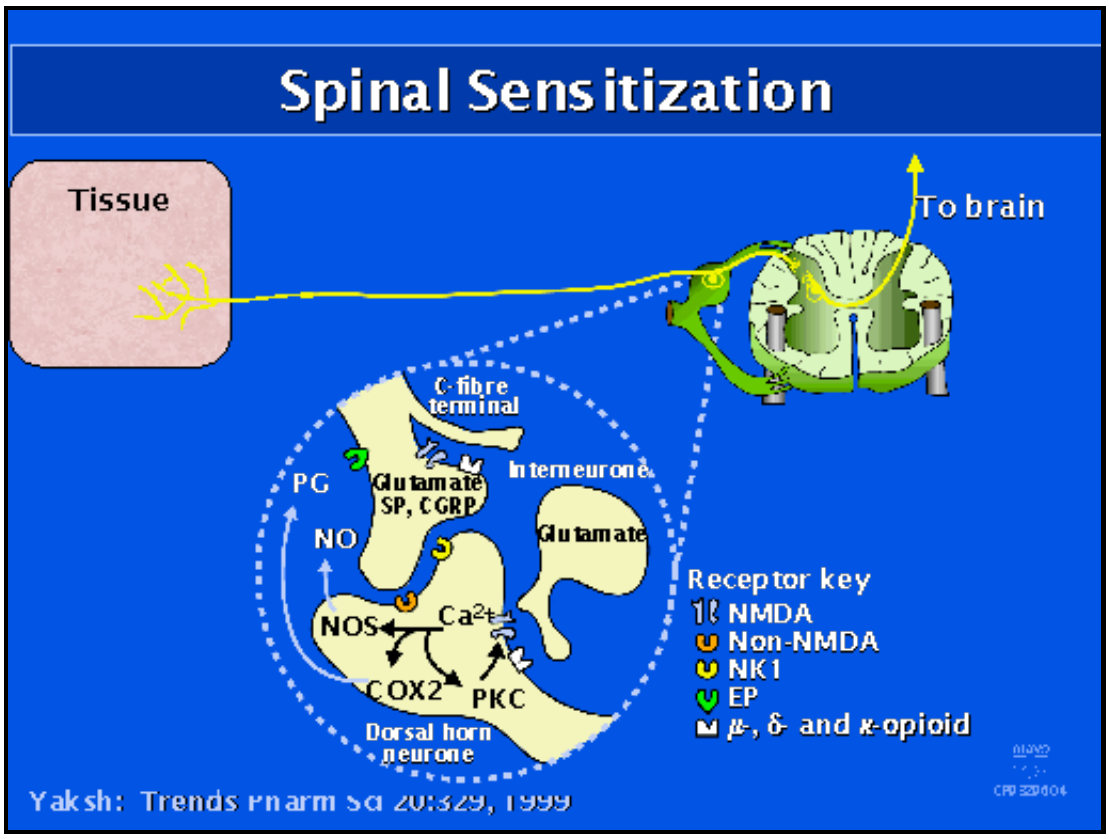

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Central spinal sensitization: mechanisms
central sensitization,

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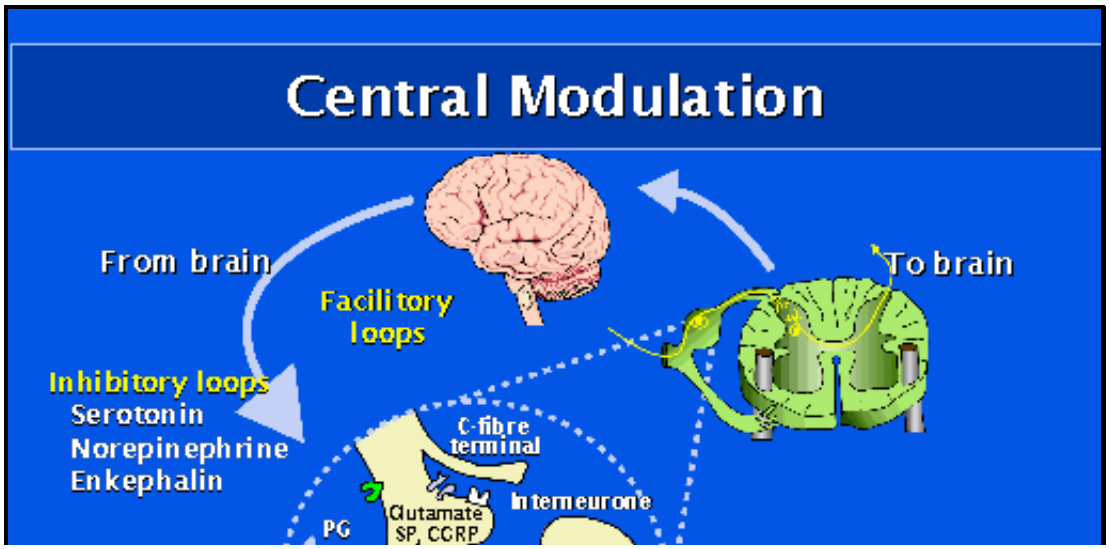

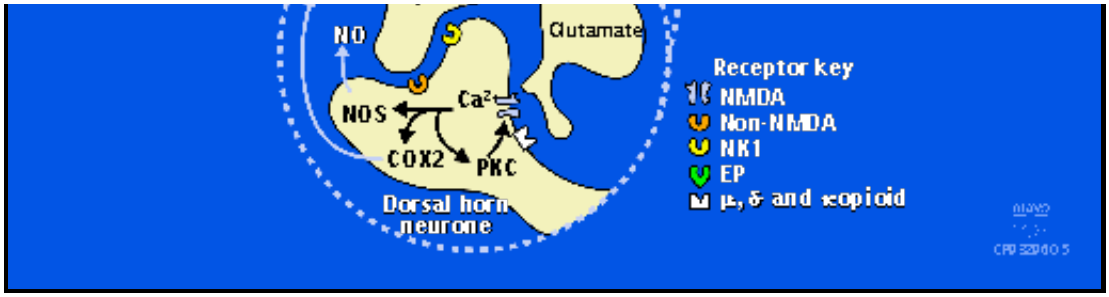

Altered central modulation: mechanisms
and altered central modulation are real phenomena which are very complicated and they are subject to very intense investigation by basic researchers and especially by pharmaceutical companies, which are very interested in developing pain medications which are more effective and have lesser side effects than the pain medications that we have now. So that is just to give you this feeling of what the activity is in this field. I don't have time to really go into detail on all these pathophysiologic mechanisms.

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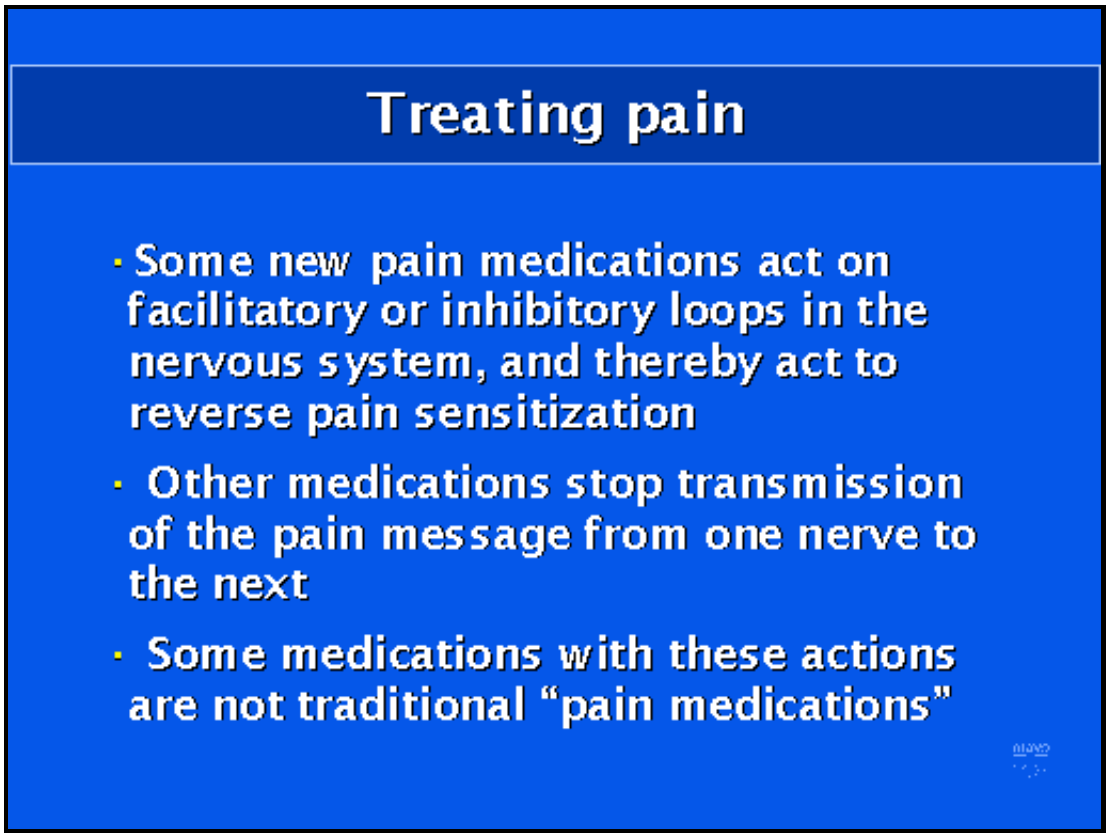

Treating pain: altering activity of neural feedback loops
One thing that I would like to emphasize is that in order to intervene and try to break this vicious cycle and try to shift this curve back to the right, with the new medications that are being developed, it is becoming increasingly important for physicians to understand the place of action of the different medications. There are medications that may act on fascilitatory loops or inhibitory loops or the transmission of the pain message from one nerve ending to the other; and sometimes a combination of medications may be particularly helpful to reduce the side effects of the medications or to increase efficiency. So this is becoming now increasingly important. There are some medications which normally are not used for pain. However, currently we know that they can help in the control of pain in chronic situations like the ones that we are discussing.

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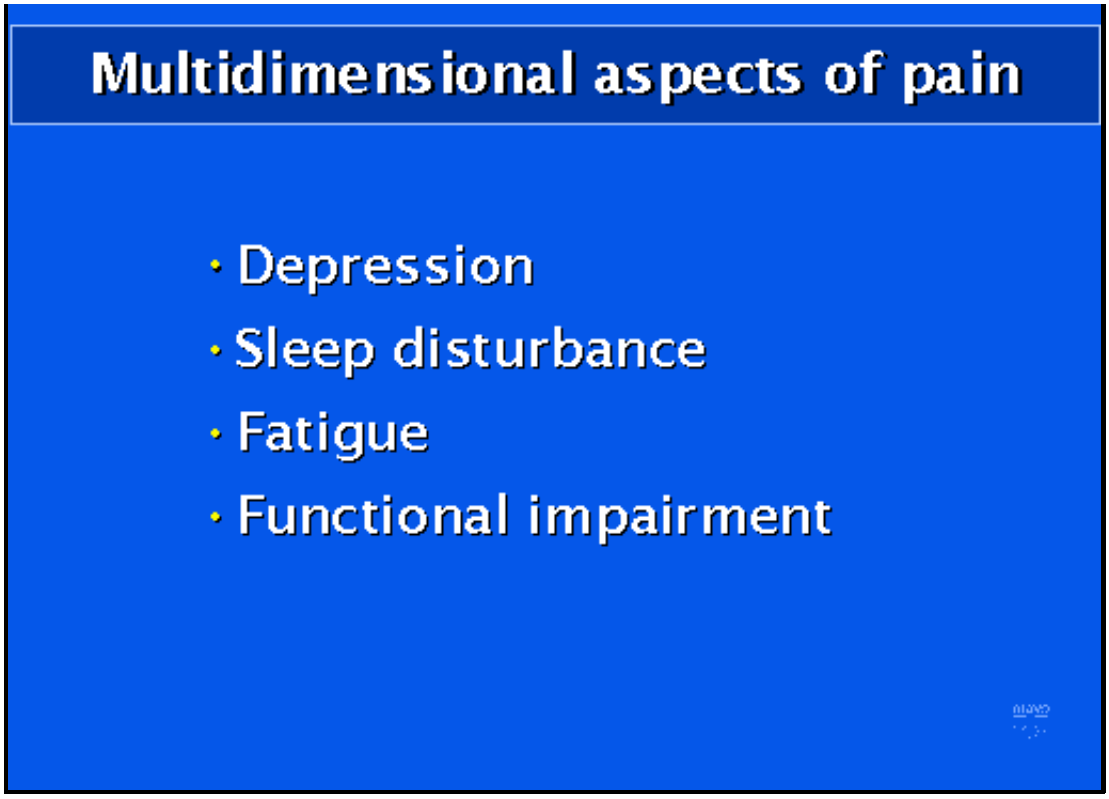

Pain has many dimensions
Another concept which is very important about chronic pain is that chronic pain is a multi-dimensional phenomenon. Patients who have chronic pain very frequently become depressed. They develop sleep disturbance, fatigue, and functional impairment. They are not capable to function normally. In dealing with chronic pain, trying to manage this problem, it is important that all of these multi- dimensions of pain are adequately addressed.

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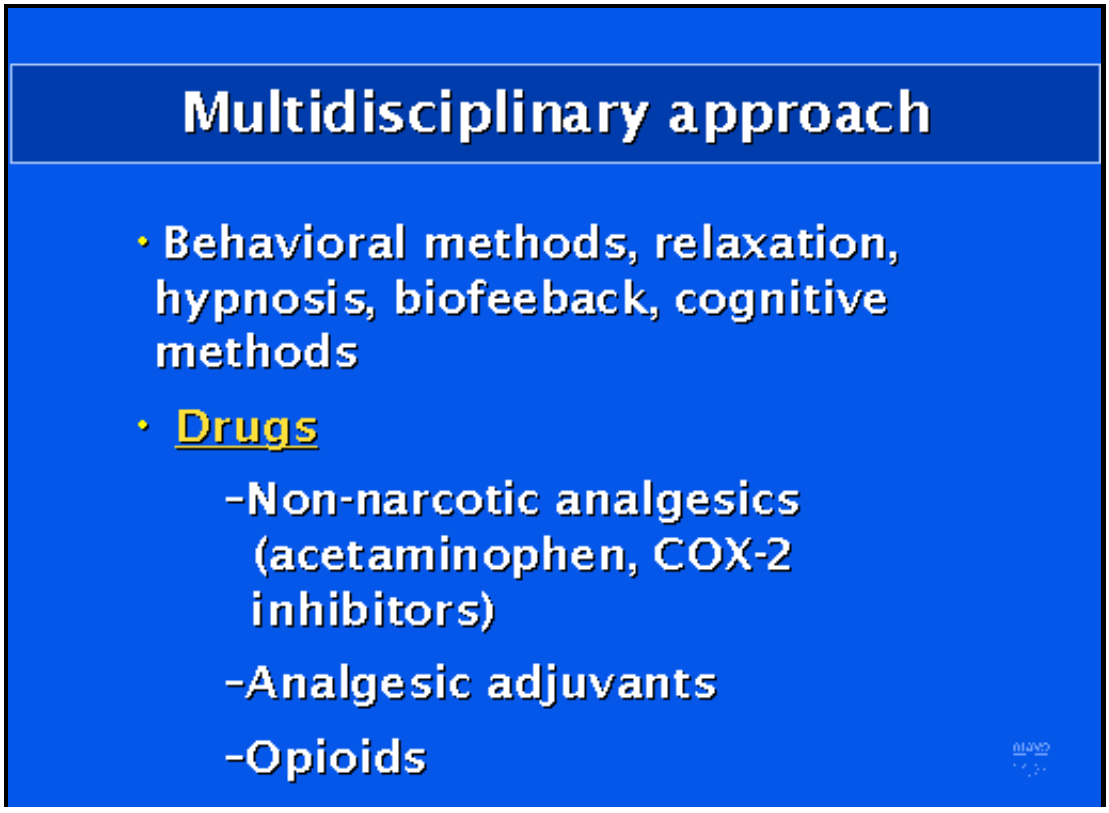

Multidisciplinary approach is required
Therefore, in order to deal with the management of chronic pain, it is important to have a multi-disciplinary approach, which includes behavioral methods, like relaxation and hypnotic techniques, cognitive behavioral therapy, which mainly means understanding better how the pain develops, and also what kind of activities can accentuate the pain, what kind of activities can relieve the pain, and biofeedback. That includes treatment with pharmacologic approaches in a step-ladder fashion, starting with non-narcotic analgesics, like acetaminophen, Cox-2 inhibitors, tramadol, and medications like these; and then using analgesic adjuvants, and there are at least five or six families of analgesic adjuvants that can be used that improve the efficiency of the analgesics. And finally, in patients who are more resistant, using either weak or strong opioids. And I will go back into that in a moment.

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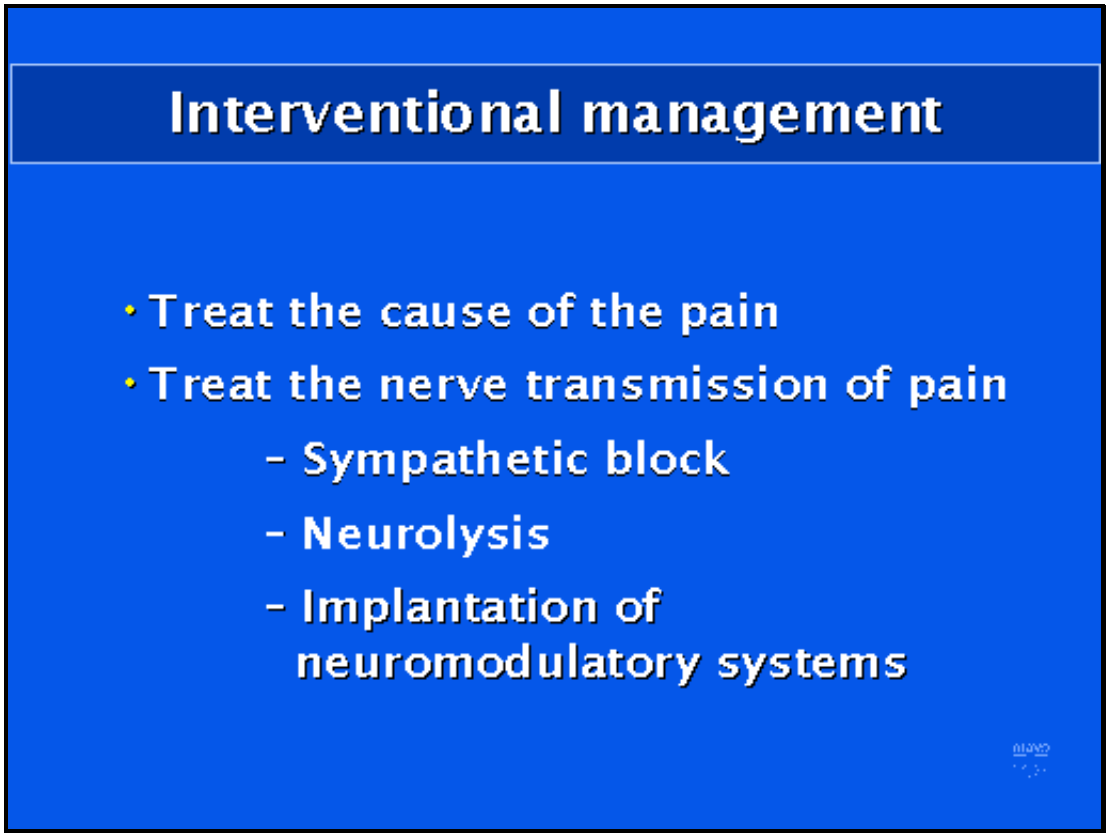

Interventional pain management
Finally, when this fails, when treatment with analgesics is necessary for prolonged periods of time, that is when more interventional pain management should be considered. These can be divided into interventions directed to treating the cysts or interventions directed to the nerve transmission of the pain, like sympathetic blocks or neurolysis, and finally in rare cares, really rare cases, implantation of neuromodulatory systems.

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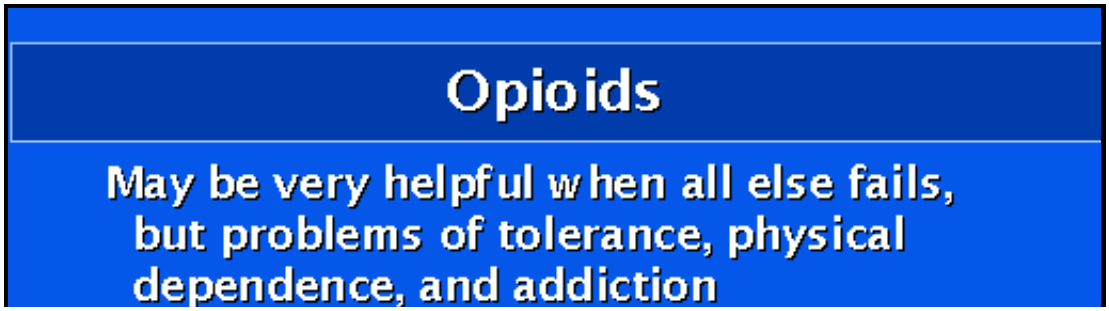

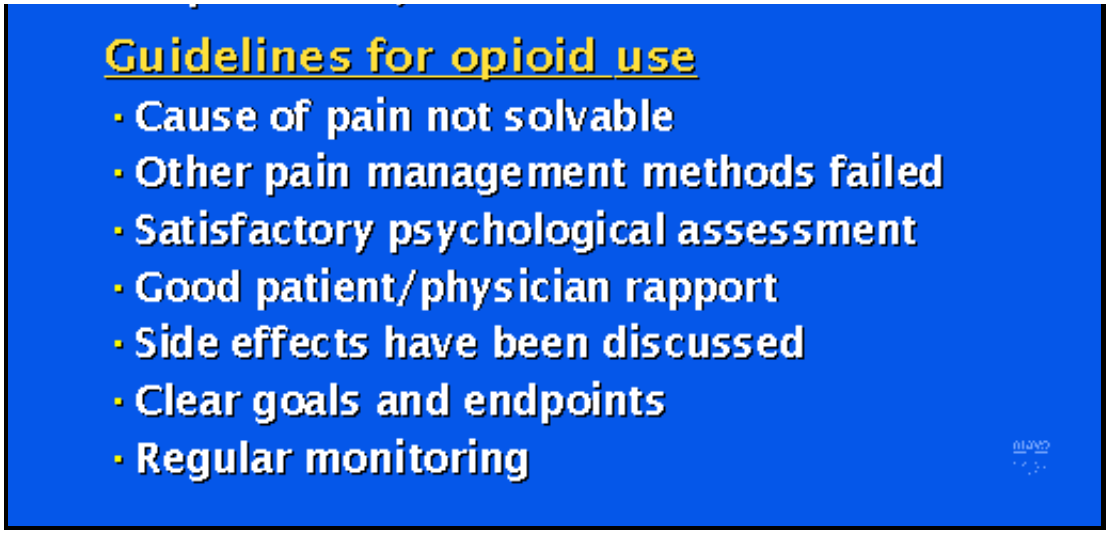

Use of opioids in pain management
One last thing that I want to mention is the issue with opioids. Opioids are very helpful in managing pain acutely. In some patients, in some selected patients, they may be very helpful in managing pain chronically. Certainly they are very helpful in managing pain in patients with terminal illnesses. But even in patients with non- terminal illnesses, they may be very helpful when everything fails in treating pain chronically. But it is important before embarking upon chronic treatment of pain with opioids to consider the problems related to treatment of pain with opioids, which include tolerance, physical dependence, and addiction. This has to be clearly discussed with the patient.

Guidelines for opioid use
There are some guidelines that have been published in the United States that need to be met when using opioids for the treatment of chronic pain. These guidelines include that the cause of the pain is not solvable, that other pain management techniques have been proven to be ineffective, the there is satisfactory psychological assessment of the patient, that there is satisfactory patient/physician rapport, that the potential side effects have been discussed with the patient, and that there are clear goals and endpoints and regular monitoring.

Concluding remarks
I think with this I will finish my part and Dr. Valente will continue with more specific information about surgical procedures.

References

1. Woolf CJ, Costigan M. Transcriptional and posttranslational plasticity and the generation of inflammatory pain. ***Proc Natl Acad Sci U S A. 1999 Jul 6;96(14):7723-30. Review.***

2. Yaksh TL. Spinal systems and pain processing: development of novel analgesic drugs with mechanistically defined models. ***Trends Pharmacol Sci. 1999 Aug;20(8):329-37. Review.***

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