Basics of Mental Health and Clinical Psychiatry
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Lecture 39
Anti-anxiety drugs

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Hello everyone, so our next topic is anti-anxiety drugs or the anxiolytics. So here we will cover the concepts like spectrum of anxiety. What are the neurotransmitters involved? And what are the mechanism of actions of various drugs.

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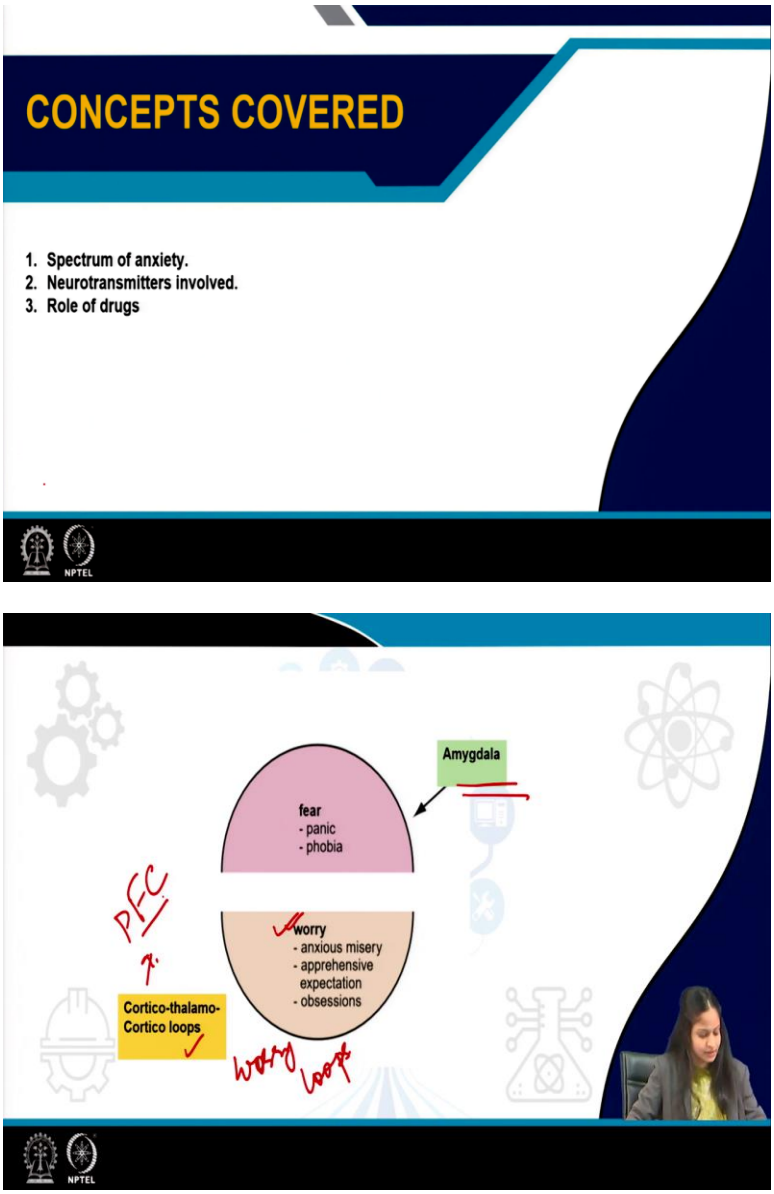

So if anxiety is a broad spectrum disorder. So if I deconstruct this syndrome anxiety we get mainly two important core components, the one is fear, the other one is worry. The fear mainly involves panic, phobia. The worry means anxiousness and apprehensive expectations and obsess, obsessions. Now these two core components are the primary features of all anxiety disorders various types of anxiety disorders but the triggering factors may be different for each.

So these are the two core components which have different pathway for various symptoms or they contribute to they attribute to different pathway. For example, the fear is mainly related to

the amygdala centered circuit mechanisms, the it has already been discussed in the limbics system lecture, how amygdala plays a very important role in developing fear.

And at the same time worry and various features of body like anxiousness, apprehensiveness, and obsessive features, they are merely contributed to the cortico-thalamo-cortico loops or corticothalamo, or striatal cortico loops or these are also known as worry loops. So when I am talking about when I am telling about cortico-thalamo-cortico loops that means this is mainly concerning with the cortex that is prefrontal cortex area.

So fear is mainly attributed to the amygdala centered circuit and body is mainly attributed to the prefrontal cortex region which is again because of the cortico-thalamo-cortico loops various loops that is the worry loops.

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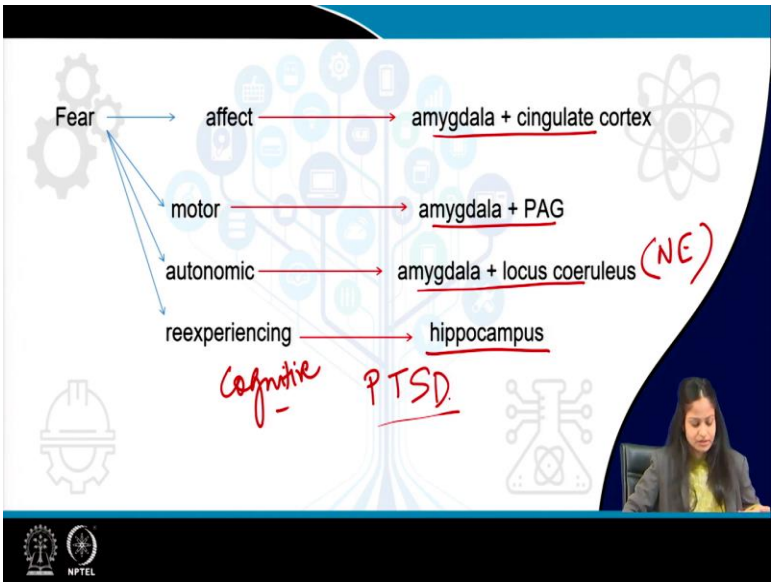

Now the various components of emotion that is fear is in emotions and the various components of emotion is the effect that is a feeling the motor component, the cognitive component, the autonomic component, let us see what are the organs or what are the structures which control them. So effect or feeling is mainly because of the amygdala and cingulate cortex. The motor components of fear is mainly amygdala and periaqueductal gray region.

The autonomic component is mainly because of the amygdala and locust coeruleus, locus coerules is the main center for the norepinephrine neurotransmitter release. And the re-

experiencing phenomenon or the cognitive function is mainly attributed to the hippocampus and this phenomenon is mainly important in case of post-traumatic stress disorder, you tend to remember the past traumatic event and you develop fear.

So that is a re-experiencing phenomenon which is mainly attributed to the hippocampus, so effect, motor, autonomic, and re-experiencing, or the cognitive phenomena. So effect is mainly because of the amygdala and the cingulate cortex. Motor is mainly because of the pericoductal gray region and the amygdala. Then autonomic is mainly because of the amygdala and the local ceruleus. And hippocampus mainly attributes to the cognitive functions.

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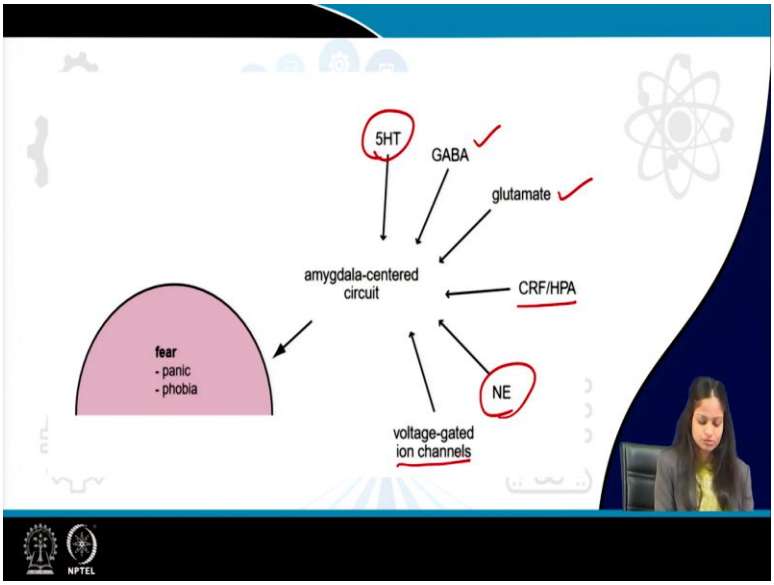

Now along with that let us see what are the neurotransmitters involved in this core symptoms, that is fear and worry. So fear we have mainly 5HT or five hydroxytryptamine that is serotonin, then we have GABA, then we have glutamate, then corticotropping releasing factor or corticotropping releasing hormone or hypothalmic pituitary axis which plays a very important role in cortisol, then we have norepinephrine and various voltage-gated ion channels. So these are the mainly neurotransmitters which attributes to the amygdala centered circuit.

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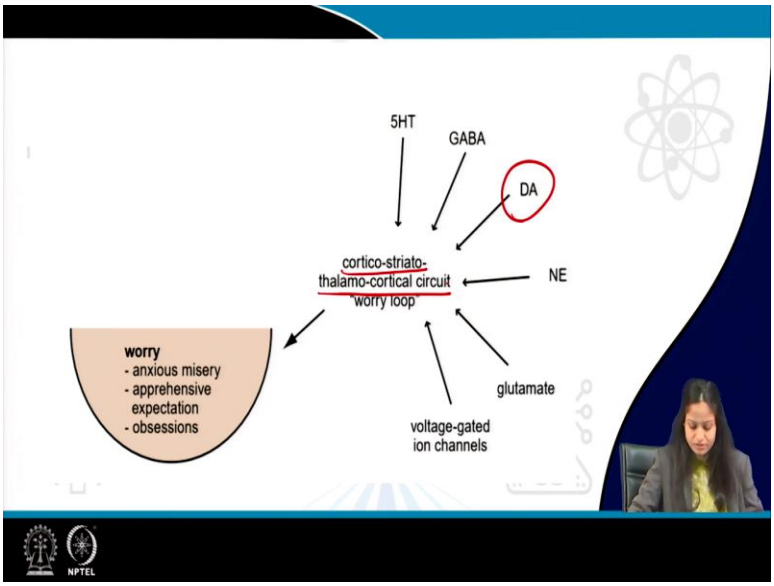

Second we have the worry. So for worry, what are the neurotransmitter, generally we have the similar neurotransmitters except one neurotransmitter that is the dopamine. So this mainly attributes to the worry loops or the cortico-striatto-thalamo-cortical circuits, these are the worry loops or attributing the prefrontal cortex regions. Besides that we have again the serotonin GABA, norepinephrine, glutamate, and voltage-gated iron channels.

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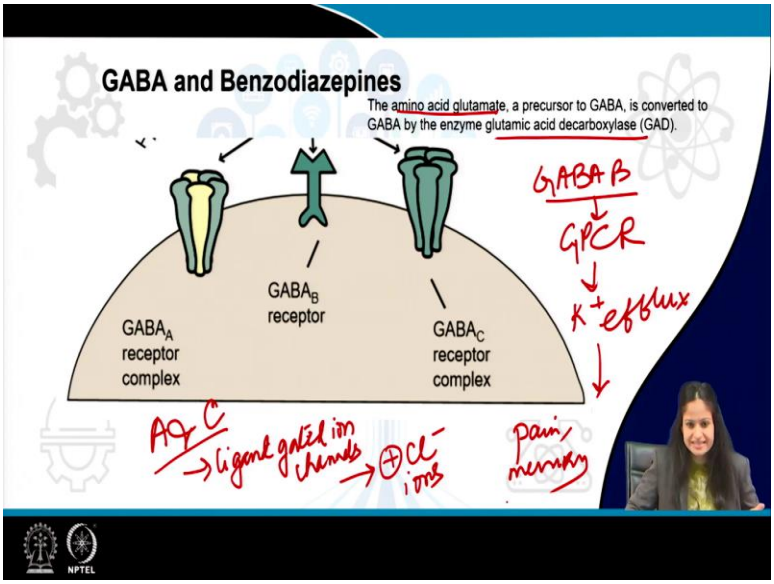

Now anxiolytic drugs, when we talk about or anti-anxiety drugs, when we talk about, mainly what we get remember that is of the benzodiazepines. The benzodiazepines is the class of drugs which mainly acts on the GABA receptors. So GABA receptors and benzodiazepines what are the mechanism of actions that will see. So GABA receptors and the GABA type of receptors are already been discussed in the neurotransmitter synapse lecture is in brief I shall revise it again, that is GABA is mainly deduced from the glutamate.

The amino acid glutamate is the precursor of GABA. And the enzyme which converts glutamate to GABA is a GAD that is glutamic acid decarboxylase enzyme. Now GABA has got three receptors mainly GABA A receptor, GABA B receptor, GABA C receptor. GABA A receptor complex, now when I am talking about receptor complex, receptor complex means there are various regions, it is not only one receptor only one unit is there that means it has got various subunits.

So as you can see in the diagram also there are various subunits in all the receptors. So GABA A receptor complex and GABA C receptor complex. So A and C, they are mainly ligand gated ion channels, ligand gated ion channels. And this will cause influx of chloride ions this will cause influx of chloride ions benzodiazepines, barbiturates, alcohol these are the three main substances which play an important role with the GABA A receptor complexes.

Then we talk about GABA B receptor GABA B receptor is mainly G protein coupled receptor. So this G protein receptor usually cause potassium efflux and this was mainly important in case of pain involvement of GABA B receptors is mainly in case of pain and memory. So this is in brief of the various GABA receptors GABA A receptor, B receptor, and C receptors we mainly deal with the GABA A receptor because that is where that benzodiazepines act.

So A and C receptors are the ligand-gated channels which mainly cause inhibition which mainly cause the postsynaptic inhibition by influx of more chloride ions and GABA B receptor is the G protein coupled receptor and that will efflux of potassium ions, whether cations are moving out or anions are moving inside anywhere, it will create inhibitory postsynaptic potential.

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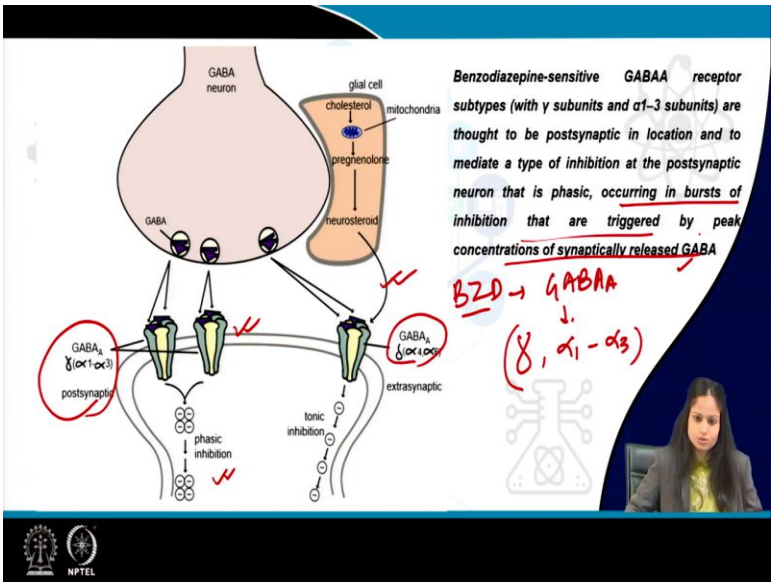

So with this we will move on to the actions of GABA on the GABA receptors on the postsynaptic membrane. So the GABA receptors are present on the postsynaptic membrane the benzodiazepines GABA receptors or the benzodiazepine sensitive GABA receptors which are present, they contain mainly the iso forms of gamma and alpha 1, and alpha 1 to alpha 3.

Now a GABA receptor as I told you it is a receptor complex, it is not a single unit, it is a receptor complex like it is not a single unit like that of a beta receptor GABA B receptor. So GABA receptor complex consists of the four transmembrane regions along with the center chloride channel and there are various the function of GABA A receptor that will depend on the which iso form or which subunits are combining.

For example there are six different alpha isomers present, there are three different beta isomers present, there are gamma isomer is there, there is delta isomer is there, whichever isomers are present that will finally attribute to its function. Benzo benzodiazepine sensitive GABA receptor usually act on the GABA A receptor, which consists of the gamma and alpha 1 to alpha 3. And this mainly contributes to the phasic inhibition.

So whenever the GABA will bind to its receptor whenever in the postsynaptic membrane, there will be a peak concentration of GABA, there will be burst of inhibition that is known as phasic inhibition. On the other hand the GABA A receptor which has got the other isomers like for

example delta isomer, alpha 4, alpha 6 isomer, their neurosteroids can bind and they cause tonic inhibitions. Tonic inhibition is a gradual slow progressive inhibitions, it does not require a certain or a peak concentration of GABA.

The phasic inhibitions is mainly triggered by the peak concentration of synaptically released GABA. So in this way benzodiazepine cause phasic inhibition.

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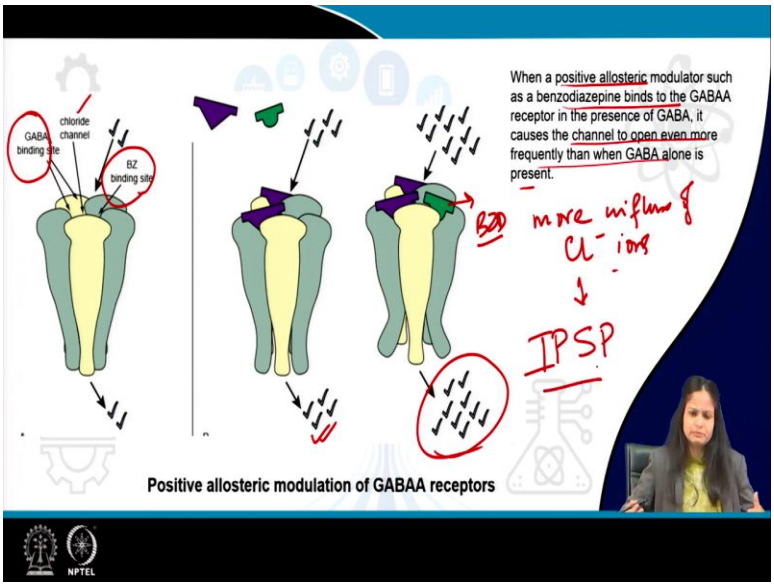

Now benzodiazepine acts as a positive allosteric modulator. So what is a positive allosteric modulator? So we can see, there is, in the receptor there is a GABA binding site, there is a chloride channel through which that will contribute to the inhibitory postsynaptic potential, and there is a different benzodiazepine binding site. So whenever a substance will bind to the receptor not the other than the original binding site of GABA.

So that is that that will cause either modulation positively or negatively. In this case it I am talking about the positive modulation means benzodiazepine will augment the activity of the GABA. Augmentation of the activity of GABA means there will be more in flux of chloride ions. Now you have to remember one thing individually if there is no GABA binding occurring in the receptor and benzodiazepine is just binding to the its own site then there will be no action at all.

For the positive allosteric modulation to occur the primary region, that is the primary pharmacological actions of the GABA has to occur, the GABA should bind to the receptor, then only the positive allosteric or the negative allosteric modulation will occur. So when a positive allosteric modulation like benzodiazepine binds to the receptor that will cause the channel to even more frequently open than when GABA is alone.

You can see the chloride channels, this is when individual GABA is binding and this green one is the benzodiazepine. And when both are binding, it is causing augmentation of the channel to open more frequently, more chloride ions, so more inhibitory postsynaptic potential, that means most there will be more or increased postsynaptic inhibition.

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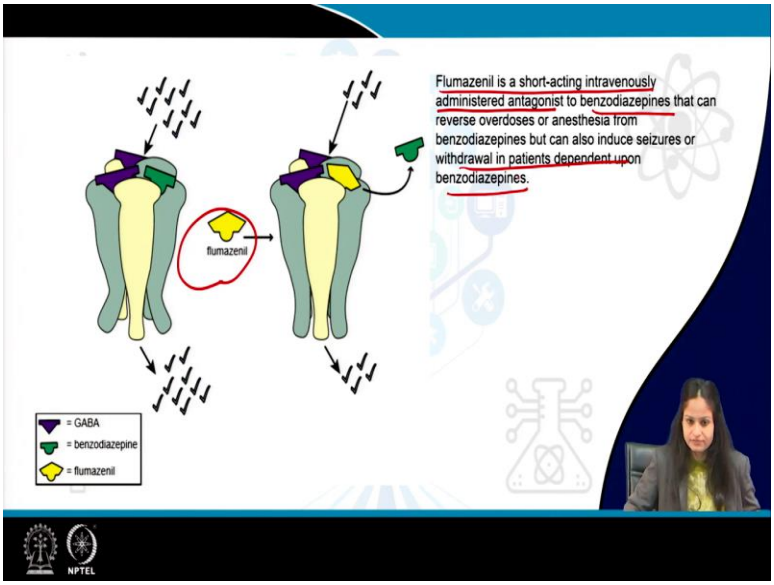

The second thing is suppose one has taken very high doses of benzodiazepines. There is, there can be benzodiazepine toxicity. Now overdose of benzodiazepine is always reversible. How it is, how it can be reversible? Now there is an antagonist for that, that is flumazenil. So flumazenil is a short acting intravenously administered antagonist to the benzodiazepines which can reverse the overdose of benzodiazepines.

Now what will happen this antagonistic of benzodiazepine that means it will competitively act on the benzodiazepine receptor, the GABA receptor will be there, but it is acting on the

benzodiazepine receptor. So again it will, it can cause the withdrawal symptoms in the patients dependent on the benzodiazepines.

Benzodiazepines the main side effect of benzodiazepine or usage of benzodiazepines is the dependence abuse and so there will be withdrawal symptoms whenever this flumazenil is used to overcome the reversal or to overcome the overdose of the benzodiazepine. So flumazenil is an antagonist and benzodiazepine attributes the role or post-synaptic inhibition by binding by positive allosteric modulation by causing more chloride ions to in get inside causing postsynaptic inhibition.

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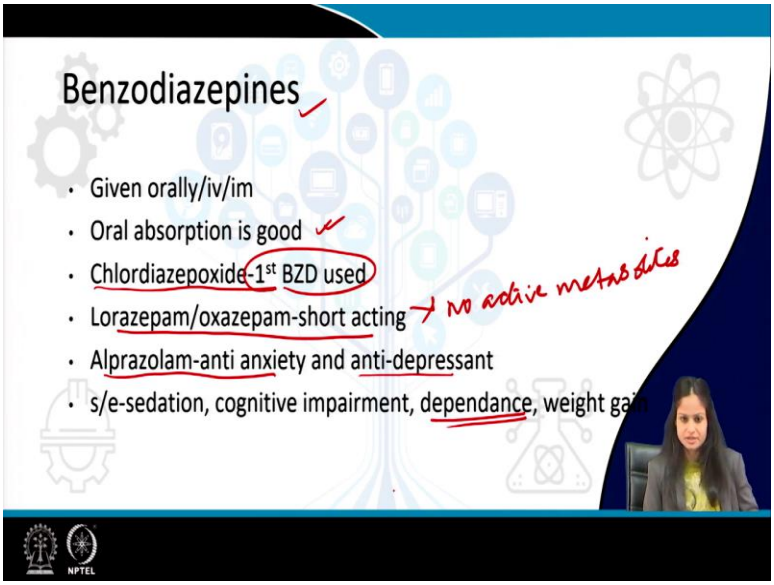

So there are various benzodiazepines in the market right now. We have lorazepam, we will have oxazepam, we have alprazolam, the (chlor) the first benzodiazepine which was used as an anti-anxiety drug or enzyolytic was chlorodiazepex chlordiazepoxide. So this is the first benzodiazepine used. Benzodiazepines are given orally or it can be given intramuscularly, the oral absorption is good lorazepam and oxyzepam is a short-acting benzodiazepine and it has got no active metabolites.

There are no active metabolites for the lorazepam and the oxazepam, alprazolam can act both as anti-anxiety drug as well as antidepressant activity and the side effects as I told you there are various side effects side effects of benzodiazepines like sedation, confusion, drowsiness,

impaired cognitive activity, but the main side effect is dependence, dependence, abuse, and the withdrawal symptoms.

That is why whenever a person is taking benzodiazepine the person to avoid the sedation, confusion, and cognitive impairment, the night doses are preferred. And whenever you want one has to withdraw the benzodiazepine drug, one should always consult the psychiatrist, and then withdraw, if you abruptly stop the dose, then you will suffer from withdrawal symptoms. So the doses should be tapered and withdrawn and on the consultation of the psychiatrist.

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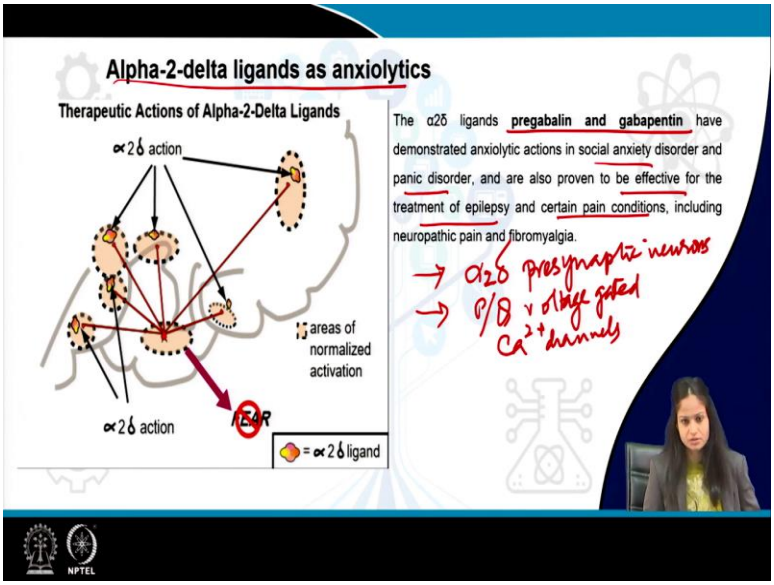

The next pair of drugs which are used as an anti-anxiety or anxiolytics are the alpha to delta ligands or they are used as anti-anxiety drugs. Now alpha 2 delta ligands, they are mainly pregabalin. We have two main important drugs GABA painting and pregabalin. The pregabalin and GABA paint in drugs, they are mainly acting on the alpha 2 delta subunits, alpha 2 delta subunits of the pre-synaptic neurons.

And also they act on the P by Q voltage gated calcium channels. Now there are various calcium channels, we have l-type calcium channels, voltage created we have t type calcium channels voltage gated. So P by Q voltage gated channels and mainly for this alpha 2 beta ligand activity. So these act on alpha 2, alpha 2 delta subunits of the present on the pre-synaptic neurons and P by Q voltage-gated calcium channels. So this is the mechanism of actions.

This alpha 2 ligands pregabalin and gabapentin, they have demonstrated anxiolytic actions in social anxiety disorder, panic disorder, they are proven to be effective for the treatment of epilepsy and certain pain conditions, chronic pain conditions like neuropathic pain or fibromyalgia. So here this alpha 2 delta ligands can be used.

Alpha 2 delta ligands are the sort of alternative to the person who are not using benzodiazepines or because of the side effect of the dependent side effect of the benzodiazepines.

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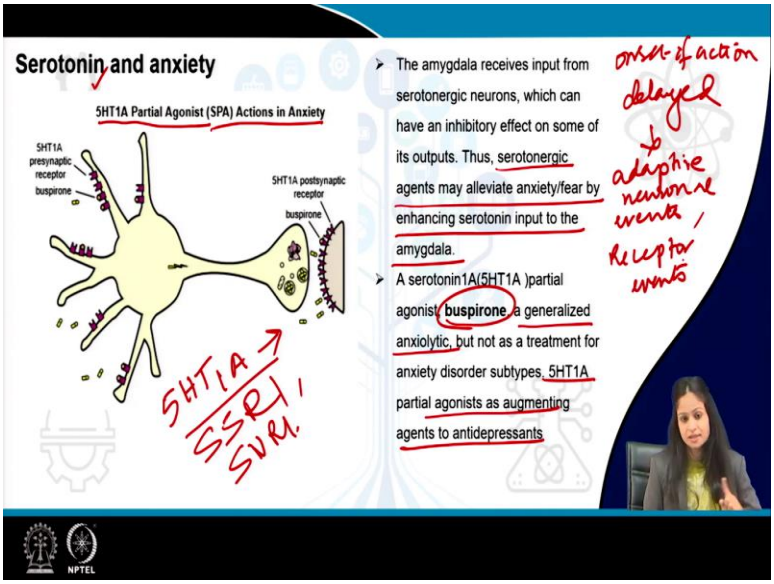

Now besides this, again the other drug which we use they modulate the neurotransmitter serotonin. Now how they will modulate the neurotransmitter serotonin. Now the serotonin object, serotonin is the key neurotransmitter which is present in the amygdala and it connects the amygdala with the prefrontal cortex, thalamus, triatum.

So this there are various certain object pathways which finally attribute to the fear and the body of the male core symptoms of the anxiety. So that is why this neurotransmitter modulation is very important and this is taken as the drug. So we have 5HT1A partial agonist actions which is used in anxiety. 5HT1A, this will cause agonistic actions this will cause increase in the serotonin level.

Now serotonin to decrease the anxiety or to decrease the symptoms of anxiety, whether it is fear or worry I have to increase the serotonin output in the synapse, that will simultaneously increase

the serotonergic neurons output to the amygdala as well as prefrontal cortex at the to the thalamus, and the striatum.

This output can be increased either by agonistic functions that means a serotonin receptor is stimulated again and again that is an agonistic functions or the serotonin reuptake transporters can be inhibited, that means the reuptake of the serotonin to the presynaptic neuron can be inhibited. So that is a function which is done by serotonin reuptake inhibitors, or serotonin non-norepinephrine reuptake inhibitors.

So they mainly cause the serotonin output or the increase in the serotonin output and thus alleviates the fear and body. So serotonergic agents will decrease the anxiety fear by enhancing the serotonin input to the amygdala. And the main important drug that is azaperones that is a partial agonist of serotonin 5HT1A that is buspirone is a generalized anxiety anxiolytic or anti-anxiety drug, it has got a partial agonist activity as augmenting agents to the antidepressants also.

Now one thing we have to remember is the action of this buspirone that is 5HT1A partial agonist is delayed, the onset of action is delayed, actually the onset of action is usually delayed. And various theories have come upon that the, this actions is delayed because the drug or the 5HT1A partial agonist is not only just not only acting just by binding to the receptors as it is seen in the benzodiazepines rather there is also receptor adaptive neuronal activity and the receptor activity.

This is mainly because of adaptive neuronal events and receptor events, there are also events which goes on there must be some events which goes on at the receptor level and the neuronal level, that is why the onset of action is delayed, that is in comparison to the benzodiazepines where there is acute onset of actions, because it when the drug binds to the receptor, it will cause the action but that is not the case with the buspirone or the 5HT1 partial agonist.

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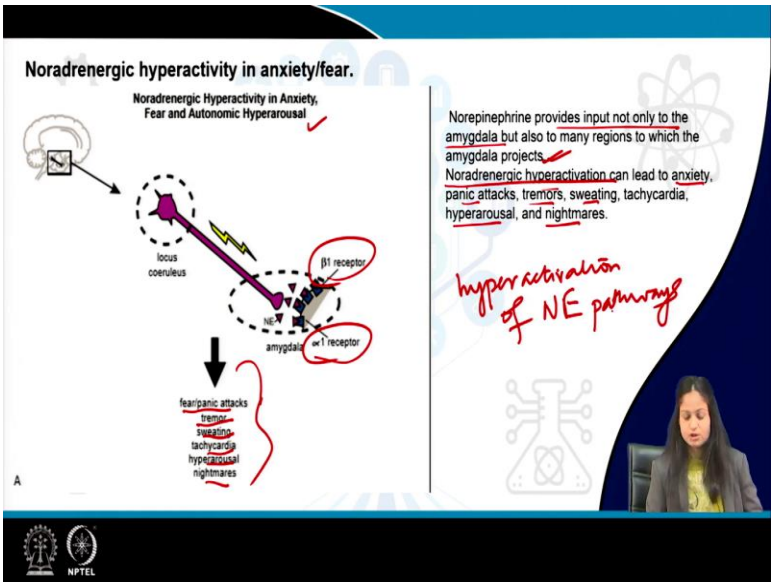

Then next we come to the noradrenergic hyperactivity in anxiety fear. Now norepinephrine is also a very important neurotransmitter, it is also a key regulator in case of anxiety disorders. Because it provides input not only to the amygdala but also to many regions to which amygdala projects that is mainly the prefrontal cortex, thalamus, and the striatum.

So what we see in case of fear, or body, or anxiety, spectrum disorders this noradrenergic hyperactivation occurs, noradrenergic hyperactivation occurs means there is excess secretion of norepinephrine from locus ceruleus. Because of this excess secretion of norepinephrine, it leads to anxiety, panic attacks, tremors, sweating various or peripheral autonomic modulation as well as there is a panic attacks, tremor, sweating, hyperarousal.

And nightmares, the fear, panic attacks, tremor, sweating, tachycardia, nightmares, hyperarousal, these are all the features where and these are mainly attributed by alpha 1 receptors or beta 1 receptors, where anyway the norepinephrine adrenaline, the receptors we know alpha and beta receptors. So in case of anxiety or fear we have to remember there is always over activation or hyperactivation of norepinephrine pathway, because of the excess secretion of norepinephrine from locus ceruleus.

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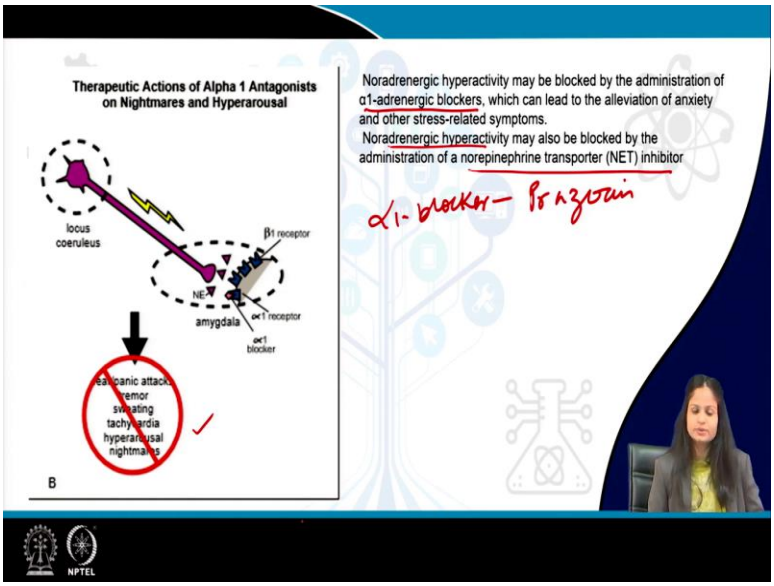

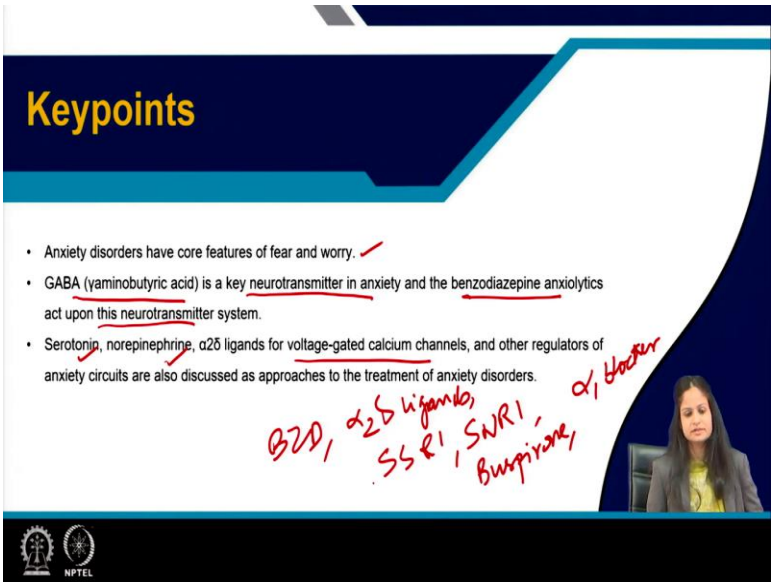

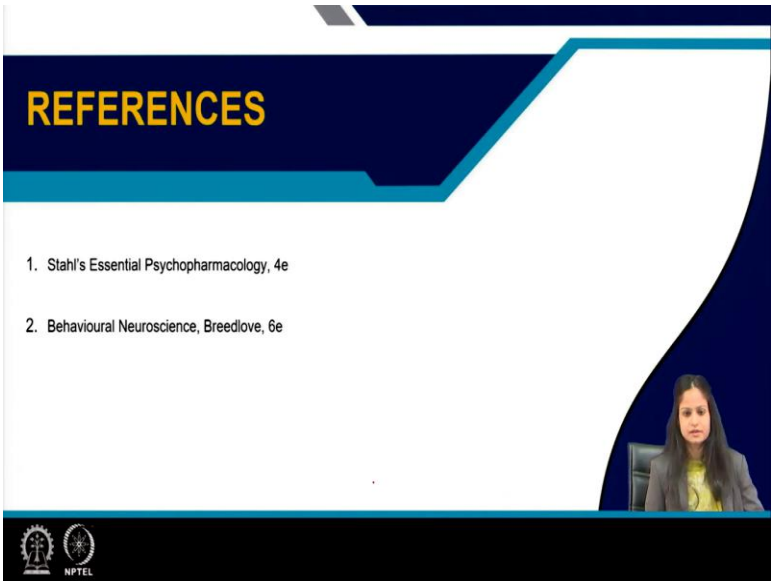

So any drugs, suppose if I want to decrease the norepinephrine secretions or if I want to prevent the binding of norepinephrine to its receptor. So I will use any receptor blocker. So the most important receptor alpha 1 blocker is used that is prazosin. So by administration of alpha 1 adrenergic blocker that leads to the decrease in the fear and other stress related symptoms or else what we can use is noradrenergic hyperactivity can also be blocked by administration of a norepinephrine transporter inhibitor.

So in the all, in every case what we are causing, we are causing the decrease in the norepinephrine release in the synapse. So that it cannot bind to its receptors and cause the fear or the worry related symptoms in the anxiety. So till now we have discovered all the first line drugs of anxiety related disorders. Generally all these drugs are used in the anxiety related disorders, because all the anxiety related disorders, they, the symptoms of, they overlap each other.

So we use benzodiazepines, alpha 2 delta ligands, then we use SSRIS, SNRIS, then we use buspiron, and alpha 1 blocker. So generally these are the drugs which we use as in the (anxio) as anxiolytics or in the anti-anxiety drugs as the first line of drugs, we have other second generation or second line of drugs also but these are the first line of drugs you have to remember.

So anxiety disorders have the core features of worry and fear. GABA that is GABA yaminobutyric acid is the key neurotransmitter anxiety and benzodiazepines mainly act upon this neurotransmitter by blocking, by not blocking by acting on the GABA receptor. And besides that

we have other neurotransmitter which are modulated that is serotonin, norepinephrine, alpha 2 delta ligands for voltage gated calcium channels mainly p q voltage calcium channels, their are also discussed at the approach to the treatment of anxiety disorders. So in anxiety disorders this much you have to remember. Thank you.