Basics of Mental health and Clinical Psychiatry
Doctor Arijita Banerjee
Doctor Bidhan Chandra Roy Multi-Speciality Medical Research Centre
Indian Institute of Technology, Kharagpur
Lecture: 37
Antidepressants

Hello everyone. So today we will start with our next topic that is Antidepressants.

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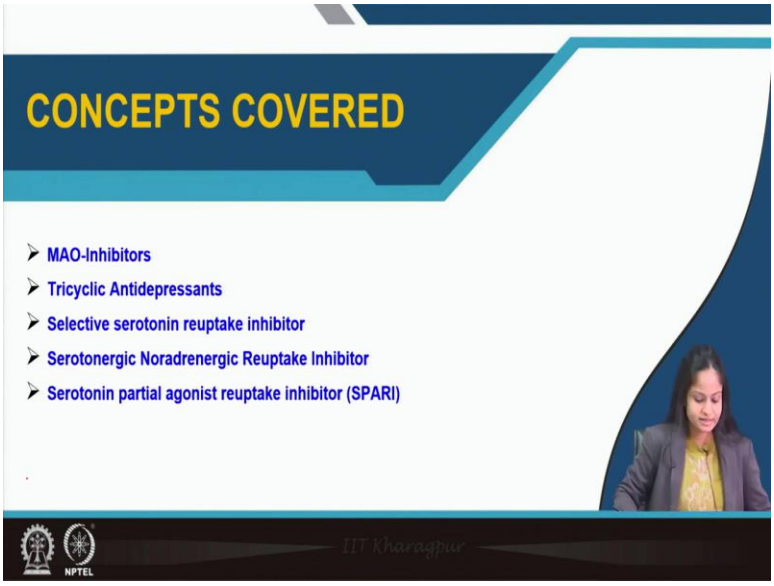

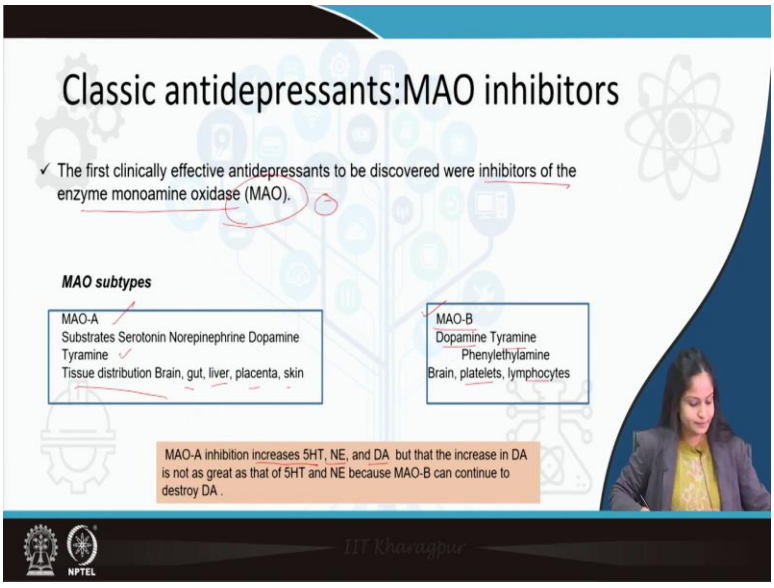

So in this topic, we will discuss various concepts like monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, selective noradrenergic reuptake

inhibitors, and SPARI that is serotonin partial agonist and reuptake inhibitors. So, under the classic antidepressants, the first clinically effective antidepressants which were discovered so, those were monoamine oxidase inhibitors.

So they are the enzymes of enzyme monoamine oxidase. Now, this enzyme has got various subtypes, we have subtype A, as well as subtype B. So, subtype A has got its substrates that means it metabolizes serotonin norepinephrine, then dopamine, tyramine, the tissue distribution our brain, gut, liver, placenta and skin. On the other hand, we have the other subtype of monoamine oxidase that is subtype B, which also metabolizes dopamine and tyramine.

Besides brain it is also present in the platelets and lymphocytes. So, if we use any inhibitor of monoamine oxidase A, that means, I am inhibiting the metabolization of this substrates, it is serotonin or norepinephrine or dopamine. So, when the metabolization of these substances will be decreased, that means, the synaptic availability will be more of these substances.

So, whenever we are using any monoamine oxidase inhibitor, so, there will be decrease in the metabolization or there will be increase in the substances in the synapses, serotonin, norepinephrine and dopamine. But, we also see that monoamine oxidase B metabolizes dopamine, it also metabolizes serotonin and non epinephrine but they metabolize serotonin and norepinephrine at higher levels.

So, whenever we are using any inhibitor of monoamine oxidase A, so, it will increase the level of serotonin, norepinephrine and dopamine but the dopamine levels will not increase to that level because it will also get destroyed by the other subtype that is monoamine oxidase B enzyme.

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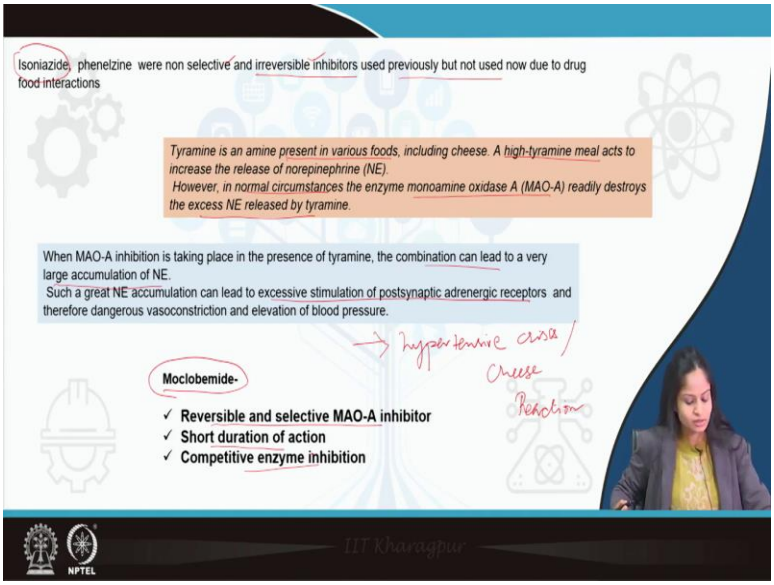

So, Isoniazide and phenelzine were non selective or irreversible inhibitors which were previously used, but the major drawback of using this monoamine oxidase inhibitors are the drug food reactions, since the tyramine is an amine, which is present in various foods particularly unprocessed cheese and meat.

So, whenever there is high tyramine level in the food, generally, if metabolization does not occur, it will give rise to accumulation of norepinephrine. So, in normal circumstances, the enzyme monoamine oxidase is there, which will destroy the excess norepinephrine which is released by the tyramine, but whenever there will be an inhibition the drugs which we are using that is monoamine oxidase inhibitor.

So, the combination of this will lead to large accumulation of norepinephrine and this large accumulation of norepinephrine will stimulate the post synaptic adrenergic receptors. So, when it will excessively stimulate the post synaptic adrenergic receptors, that will cause dangerous vasoconstriction and elevation of blood pressure, the blood pressure will raise to a higher level and this will cause hypertensive crisis.

And this is also known as cheese reaction, because, it usually occurs on consumption of unprocessed cheese if the person is taking monoamine oxidase inhibitor. So, this is also known as cheese reaction. So, hypertensive crisis or cheese reaction, now, as I had already told you that

these are the selective this is a non selective irreversible inhibitor which was first discovered in an antituberculosis drug that has Isoniazide.

So, to prevent or to reduce the side effects the reversible inhibitor was discovered that is moclobemide. It is a reversible selective monoamine oxidase A inhibitor it has got shorter duration of action, and it is a competitive enzyme inhibitor but still the side effects are there though it is reduced to some extent, but because of the side effects, so this drug is not used anymore nowadays. So next we will move on the tri cyclic antidepressants.

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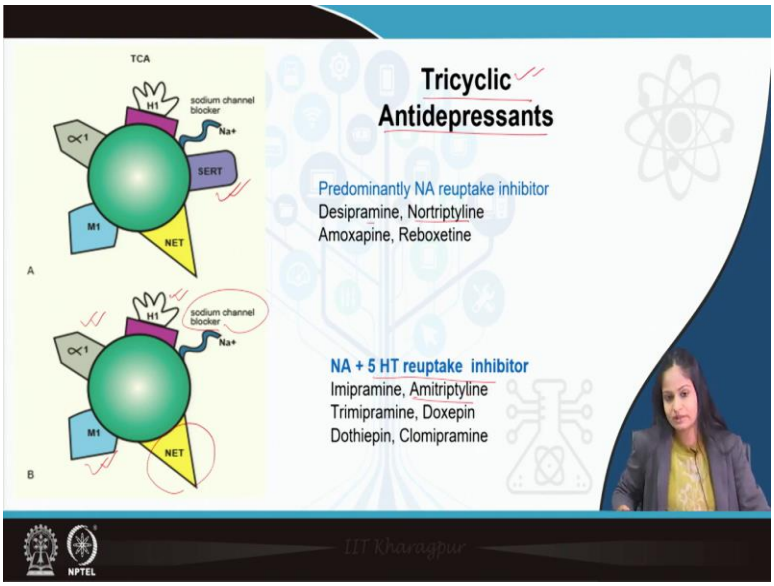

Now, tri cyclic antidepressants, the name tri cyclic because it bears three rings. So, predominantly tri cyclic antidepressants as we can see from the figure they are the this NET is norepinephrine reuptake inhibitors or norepinephrine pump transport inhibitors. So, they usually inhibit the norepinephrine pump transport, they are antagonistic of the M1 that is muscarinic cholinergic receptor.

They are antagonistic to the alpha 1 adrenergic receptor and they are also antagonistic to the H1 histamine receptors. Besides this all tri cyclic antidepressants also block sodium channels voltage gated sodium channels. So, these are the predominantly norepinephrine reuptake inhibitors which fall under tri cyclic antidepressants that is Desipramine or Nortriptyline.

These are few examples you can remember some tri cyclic antidepressants also have serotonin reuptake inhibitors or serotonin reuptake of serotonin pump transport inhibitors. So, this besides the norepinephrine reuptake inhibitors and besides all the inhibitions, they are also 5 HT reuptake inhibitors or serotonin inhibitors reuptake inhibitors we have those drugs like Imipramine, Amitriptyline, Dorthiepin, Doxepin these are the drugs which has got both norepinephrine as well as 5 HT reuptake inhibitors.

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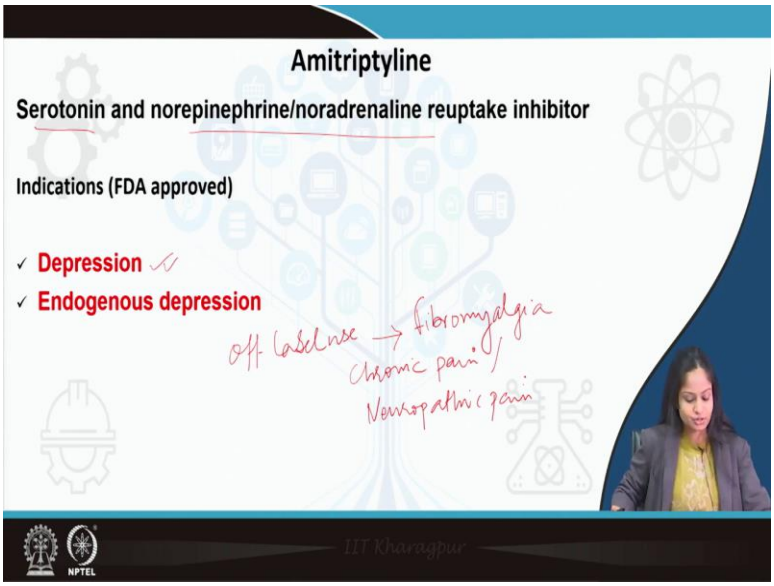

Now as I told you this amitriptyline is both serotonin and norepinephrine reuptake inhibitors these are mainly used in depression, endogenous depressions now 75 percent of the depressions are associated with stressful incidents in our life. But endogenous depression is 25 percent of the depressions which are not associated to any stressful events.

So, when the depression is associated with stressful events, the mainly symptoms we have along with depression, low mood and all we get anxiety and agitations. So, that is also known as reactive depressions. 75 percent of the depressions are like that, but whenever the depression is not associated to any stressful event that is endogenous depressions.

Now, this drug is indicated in this besides we have other off level use of amitriptyline, this is used in fibromyalgia. This is also used in chronic pain, or neuropathic pain. So these are the off label use of amitriptyline that has fibromyalgia, chronic pain or neuropathic pain besides the depression and endogenous depressions.

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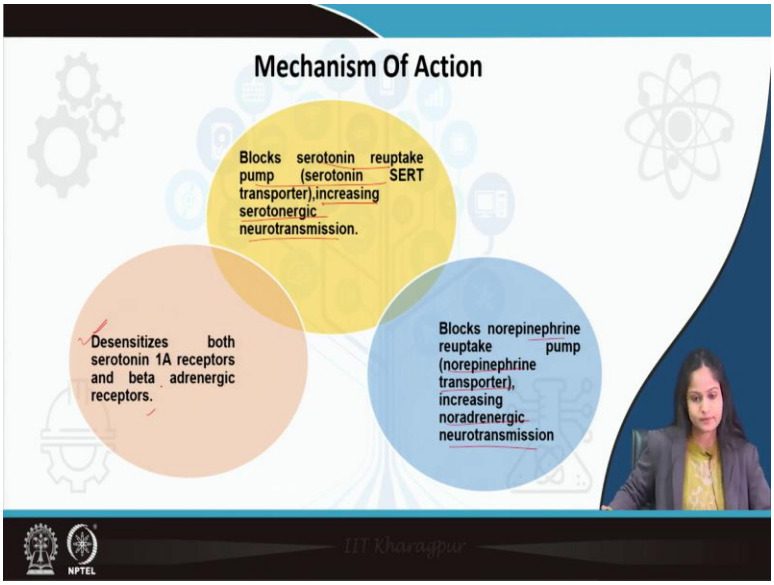

Now, what are the mechanism of action of tri cyclic antidepressants as we had seen from the diagram, the blockade of various transporters, so the first block is the serotonin reuptake pump, serotonin reuptake pump or the serotonin reuptake inhibitors. So finally, when I am blocking means, I am actually causing the substance to increase in the synaptic level.

So, there will be increase in the serotonergic neurotransmission. The second mechanism of action is blocking of the norepinephrine reuptake pump or the non epinephrine transporter. So, that will cause increase in the neuro adrenergic or nor adrenergic or norepinephrine neurotransmission then there is desensitization or downregulation of the serotonin 1A receptors as well as beta adrenergic receptors.

So, these are the mainly three mechanisms by which tri cyclic antidepressants, attributes to its pharmacological actions, leading to both benefits as well as side effects.

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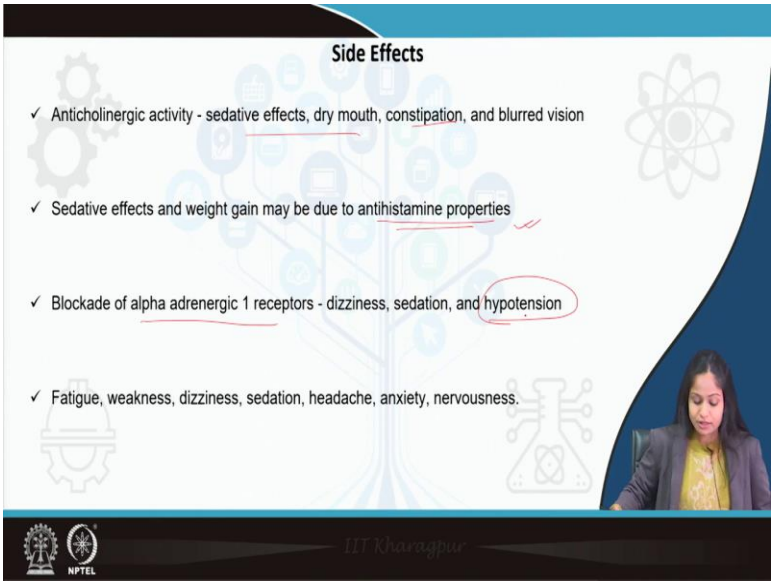

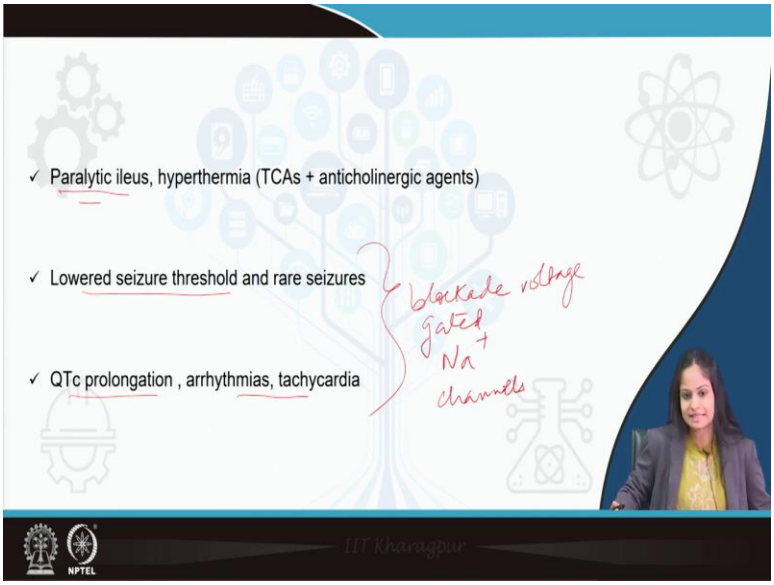

Now, mainly the side effects from the diagram we had seen it blocks the M1 muscarinic or cholinergic receptor. So the anticholinergic side effects are mainly dry mouth, blurred vision, then constipation, sedative effects, the weight gain is mainly due to the antihistaminic properties whenever the person is using tri cyclic antidepressants.

So mainly the main concern lies with the weight gain of that person in long term use there is weight gain, so that is mainly attributed to the antihistaminic properties. Now block it off alpha 1 receptors, alpha 1 adrenergic receptors, they mainly result in hypotension, hypotension as decreased blood pressure.

So, fatigue, weakness, dizziness, sedation, nervousness, these are all because of the Alpha 1 adrenergic receptors. Paralytic ileus is again due to the anticholinergic properties. Some report where there of rare seizures and cardiac arrhythmias. Now, cardiac arrhythmias that is irregular heart rates, tachycardia increased heart rate and QTc prolongations.

And the seizures activity that is lower seizure threshold. These all are because of the blockade of voltage gated sodium channels, voltage gated sodium channels. Now, in the first diagram, we had seen that there is a blockage of all the tri cyclic antidepressants, they block the voltage gated sodium channels.

And we know sodium ion is very important for the membrane potential and the action potential so, obviously impulse conductions will get deranged and that will result in abnormal electrical activity both at the level of brain as well as the level of heart. So, that results in the seizures activity as well as the arrhythmia.

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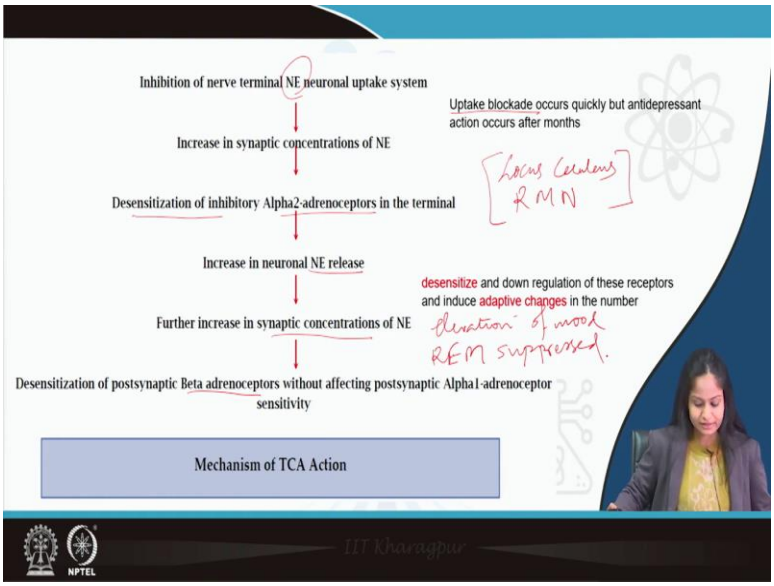

So, next we will come to the other drug that is Dothiepin. This is also serotonin and norepinephrine reuptake inhibitor which is mainly indicated in major depressive disorder, then anxiety, neuropathic pain or chronic pain and treatment resistant depression. So what is the actually the mechanism of tri cyclic antidepressants.

Now the initial mechanism the initial effect which occurs because of the administration of tri cyclic (administrate) anti depressants is the decreased firing at the level of locus ceroleus, and Rafi Magnus nucleus. Now locus ceroleus or Rafi Magnus nucleus, these are very important because they play an important role in the neurotransmitter norepinephrine as well as serotonin respectively.

So, inhibition of the non terminal norepinephrine neuronal reuptake system will occur. So the uptake blockade when it occurs, it will occur very quickly, but the antidepressant action takes place in months. So, if the person is taking an tri cyclic antidepressant, generally in 1 or 2 weeks, we do not get to see the action or the effect, it takes usually a month to see the effect.

So, the inhibition of nerve terminal norepinephrine neuronal uptake, there will be blocked of this norepinephrine uptake that will result in the increased concentration of norepinephrine in the synap. So, after this there will be desensitization or downregulation of inhibitory alpha 2 adrenergic receptors in the terminal that will further cause increase in the norepinephrine release, further norepinephrine released will occur in the synaptic concentrations.

And that will cause desensitization or downregulation of the beta post synaptic adrenergic receptors without affecting the alpha 1 adrenergic receptors. Now, because of this desensitization and downregulation of this receptors, they induce various adaptive changes like there will be elevation of the mood, which happens over a month elevation of mood, then the REM REM sleep will get suppressed and there will be fewer night awakenings. So, in this way, there is a tri cyclic antidepressants mechanism of actions which is brought about in a month.

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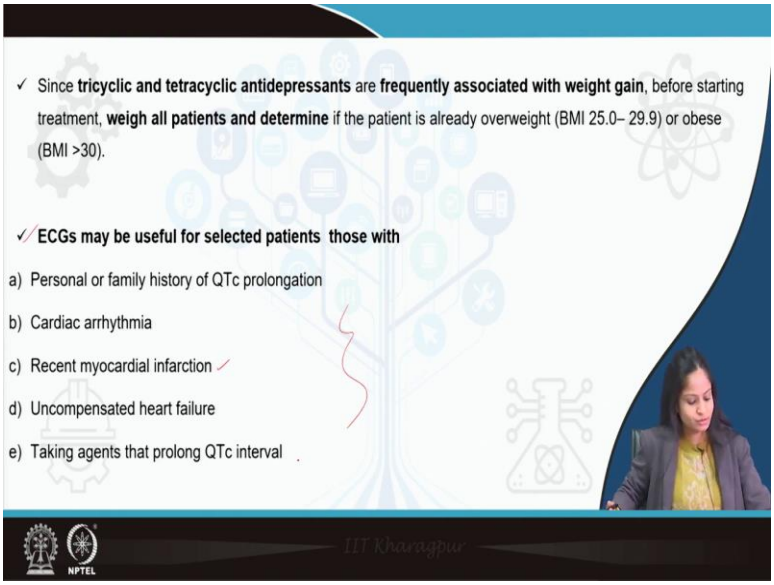

Now, try cyclic antidepressants when they are prescribed various things we are supposed to keep in mind that is the weight of the person whether that person falls under the obese category or overweight category, then the most important thing is we have to check the cardiac profile cardiac profile because as it has been told the drug is associated with the cardiac arrhythmias.

So, ECG is very useful for selected patients those who are having family history of cardiac disease, those who are having family history of QTc prolongation or they are using any drugs which could prolonged the QTc interval. If there is any cardiac arrhythmias known cardiac arrhythmias in the patient.

If there is any recent myocardial infarction, if there is any uncompensated heart failure, so, this we have to keep in mind and prescribe the drugs. So, and the patient if it is overweight and obese then we have to check that also along with the diagnosis of along with various tests like lipid profile and cholesterol level.

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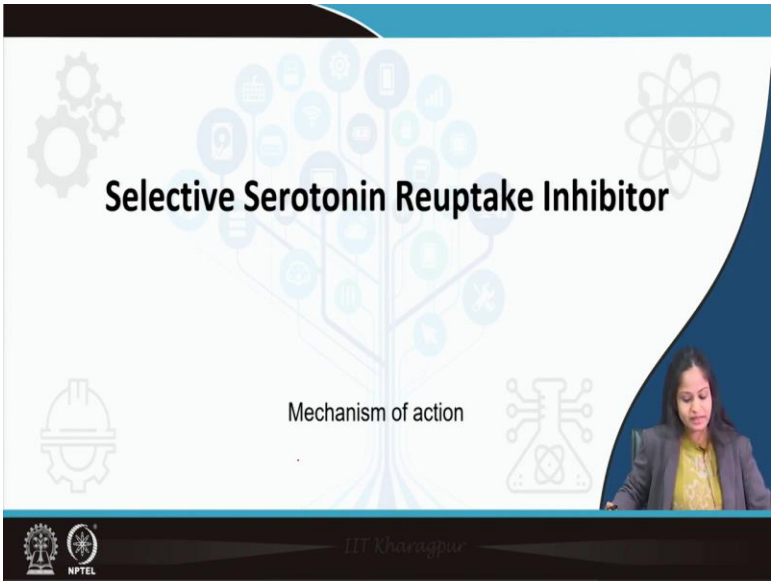

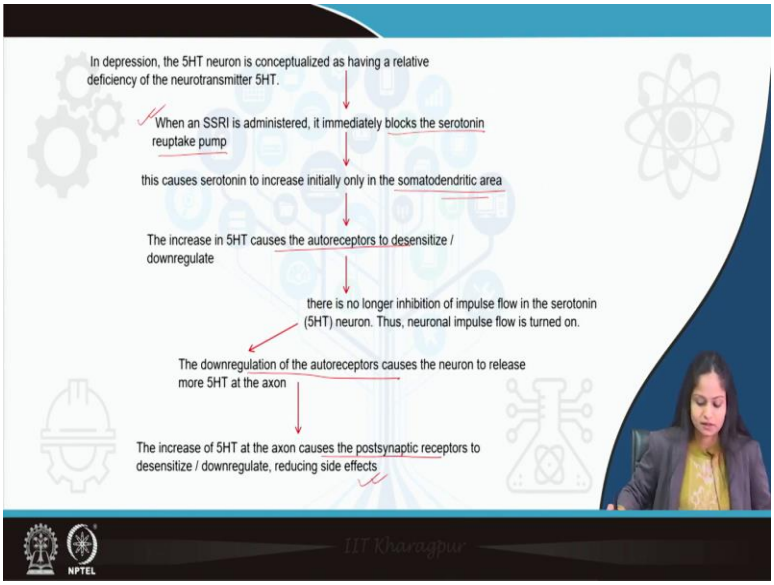

Next drug is the selective serotonin reuptake inhibitors. So, the mechanism of action of selective serotonin reuptake inhibitors is in depression it is usually seen that the serotonin level in a serotonergic neuron is depressed. So, I have to make the serotonin output increased. So, how I will do that by giving by administering. A serotonin reuptake inhibitor or by blocking the serotonin pump transporter.

So, when the serotonin reuptake inhibitor is administered, it immediately blocks the serotonin reuptake pump when the serotonin transporter is blocked. So, there will be more availability of the serotonin or 5HT in the somatodendritic area initially it will be more in the area of the

somatodendritic region the increase in 5HT cause the desensitization or down regulation of auto receptors 5 HT auto receptors.

So, finally, there will be no longer inhibition of the impulse flow in the serotonin neuron. So, because of this the impulse is turned on and there will be serotonergic neurotransmission. After this there will be down regulation of the auto receptors which will cause further release of serotonin at the xzonal level. Now, when this xzonal level serotonin will get released, there will be again down regulation or desensitization of the post synaptic receptors.

And this post synaptic receptors we will reduce the various side effects. So, in this way, SSRI acts in our body.

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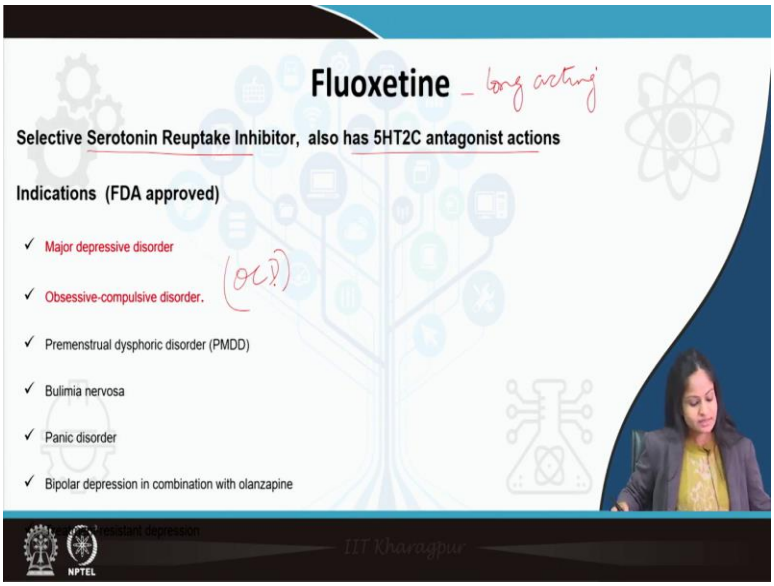

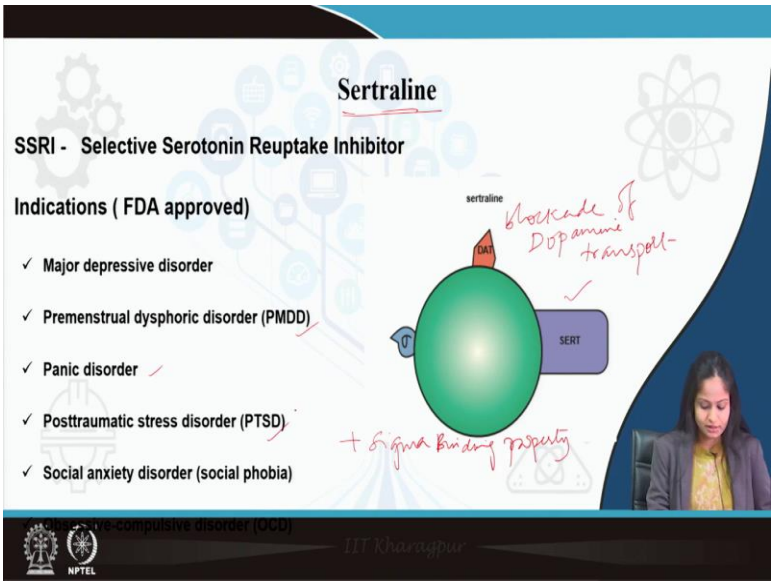

Now, the very important drug which is used, it plays a dual role. It is a selective serotonin reuptake inhibitor, as well as it has 5HT2C antagonistic actions. And fluoxetine is a long acting, SSRI, which is used. The major indications are major depressive disorder, OCD or obsessive compulsive disorder, premenstrual dysphoric syndrome, panic attacks, panic disorder, bulimia nervosa, so, these are the main indications of fluoxetine which is a long acting SSRI, then we have another drug that is sertraline.

So, as we can see from the diagram, besides the serotonin reuptake inhibitor or the serotonin pump blockade it also has got binding property of sigma, sigma binding property it also causes blockade of dopamine transport. So, when dopamine transport is blocked, that means it will cause the availability of dopamine also in the synapse more. So, the indications of sertraline is major depressive disorder, premenstrual dysphoric disorder, panic disorder, posttraumatic stress disorder and social phobia. So, these are the main indications of sertraline.

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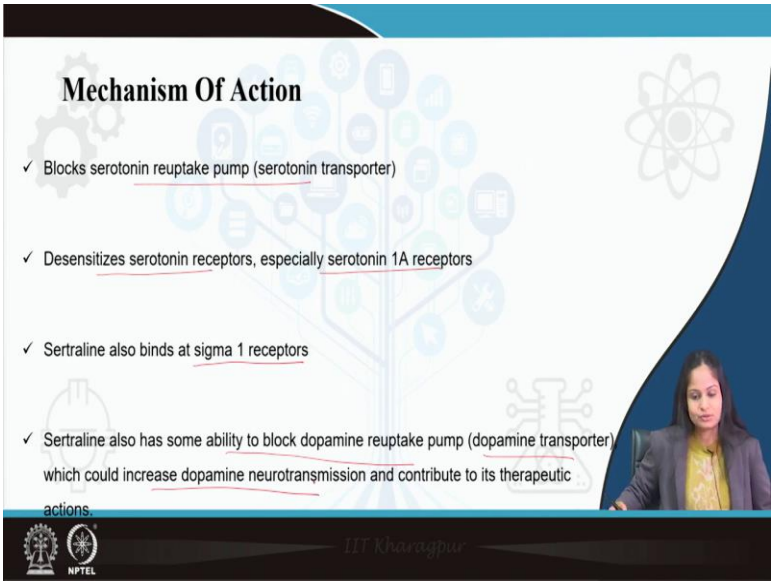

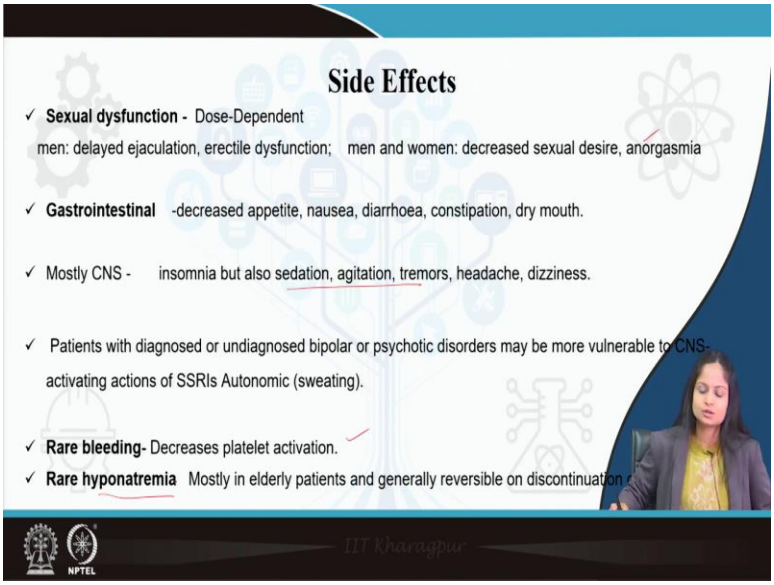

The mechanism of action is first already been told it is blocked a serotonin reuptake pump that is serotonin transporter, as well as it desensitizes the serotonin receptors specially the serotonin or 5HT1 receptors. It also binds at the sigma 1 receptors, sertraline has got an ability to block the dopamine reuptake pump that is a dopamine transporter which we could cause increase in the dopamine Neurotransmissions and contribute to its therapeutic effects.

So, these are the mechanisms of sertraline. The side effects of the drugs are mainly dose dependent. So sexual dysfunction is one of the side effects of this SSRI in males it cause delayed ejaculation and erectile dysfunctions in case of both male and females there is loss of libido

decreased sexual desire or anorgasmia there is gastrointestinal upset nausea, vomiting, diarrhea, constipation, decreased appetite.

There is insomnia but also there is sedation agitation, tremors, headache, dizziness, there is autonomic sweating there can be rare bleeding problems because of increased platelet activation, aggregation time that is decreased platelet activation, there is rare phenomenon of hyponatremia mainly in elderly patients that is also reversible if we stopped the drug.

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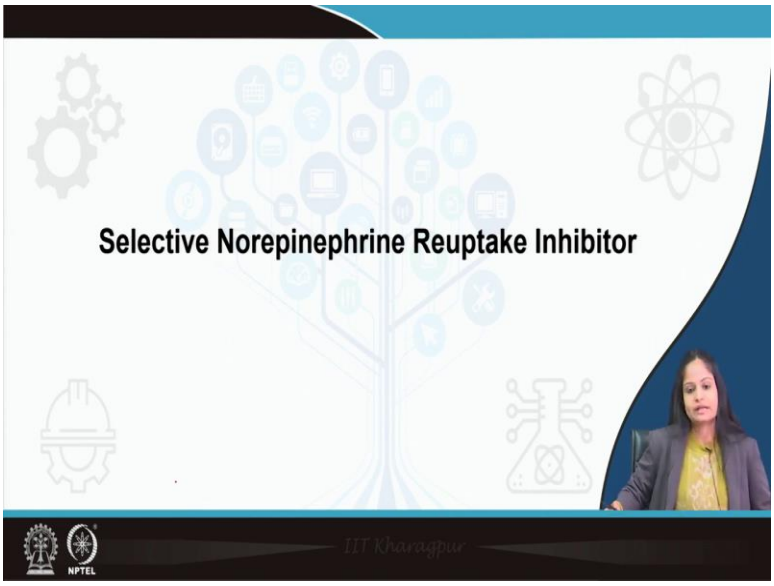

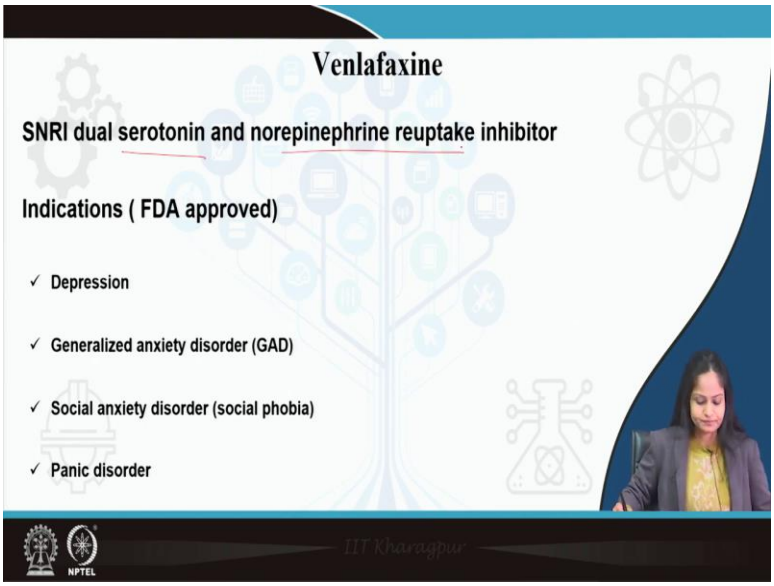

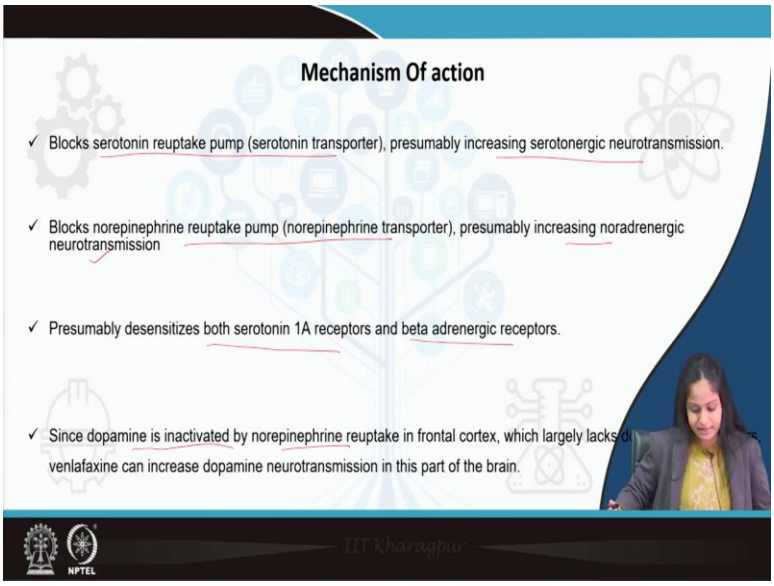

Now, the next group of drugs is selective norepinephrine reuptake inhibitors or SNRI. The main drug we have venlafaxine it is also playing a dual role because it is a serotonin reuptake inhibitor as well as norepinephrine reuptake inhibitor. The indications are depression, generalized anxiety disorder, social phobia, panic disorder.

So depression as well as an anxiety disorder is just used. The mechanism of action of this drug is first one that is serotonin reuptake pump inhibitor the serotonin transport is blocked. So, that will cause obviously the increase in the serotonergic neurotransmission. That second one is the norepinephrine transporter blockade.

So when the norepinephrine reuptake pump or transporter is blocked, that will again increase the noradrenergic neuro transmission. So with that it desensitizes both serotonin 1A receptors as well as beta adrenergic receptors. Now, since dopamine is inactivated by norepinephrine reuptake, the norepinephrine transporter also causes the reuptake of dopamine so but here when we are using a blockade of norepinephrine transporter, so the dopamine is also made available mainly in the frontal cortex and hence it causes or it enhances the dopamine neurotransmission in the brain.

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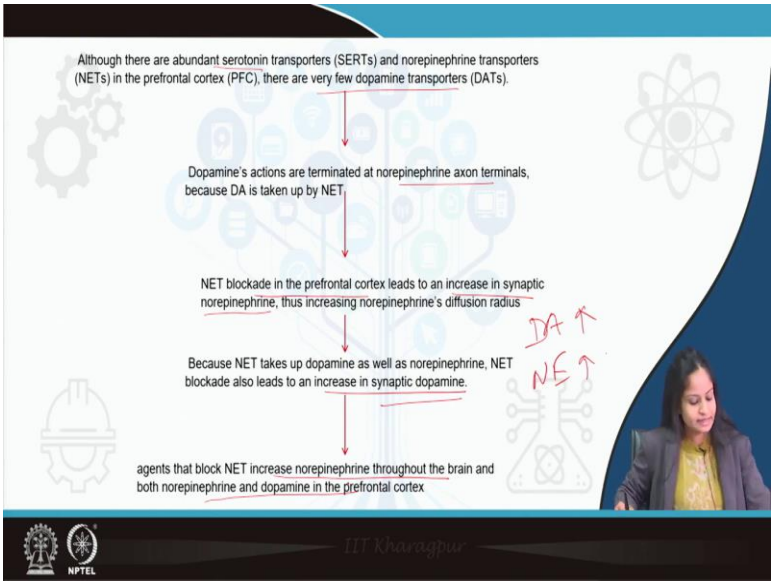

So that has been told in that flowchart form. There are abundant serotonin receptors and norepinephrine receptors in the brain. We have serotonin as well as norepinephrine transporters. But in the frontal cortex, the dopamine transporters are very few. So dopamine sections are terminated at the norepinephrine axon terminals, because usually the uptake of dopamine is done by the norepinephrine transport pump.

But whenever there is a blockade of this norepinephrine transporter pump in the prefrontal cortex area, which is a main site for cognition, so that will lead to an increase in the synaptic norepinephrine as well as the dopamine. So there will be increase in the dopamine as well as in the norepinephrine level. So this agents will not only increase the norepinephrine throughout the brain, but also norepinephrine and dopamine in the prefrontal cortex, and that will attribute its pharmacological actions.

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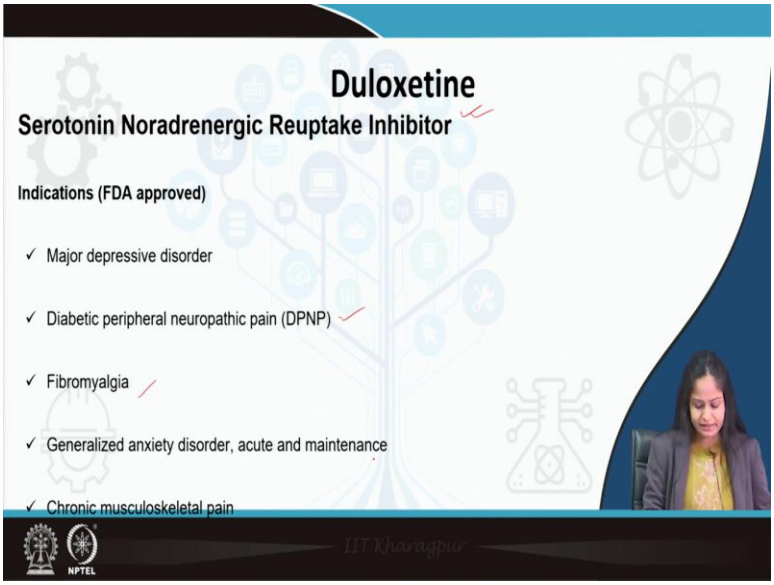

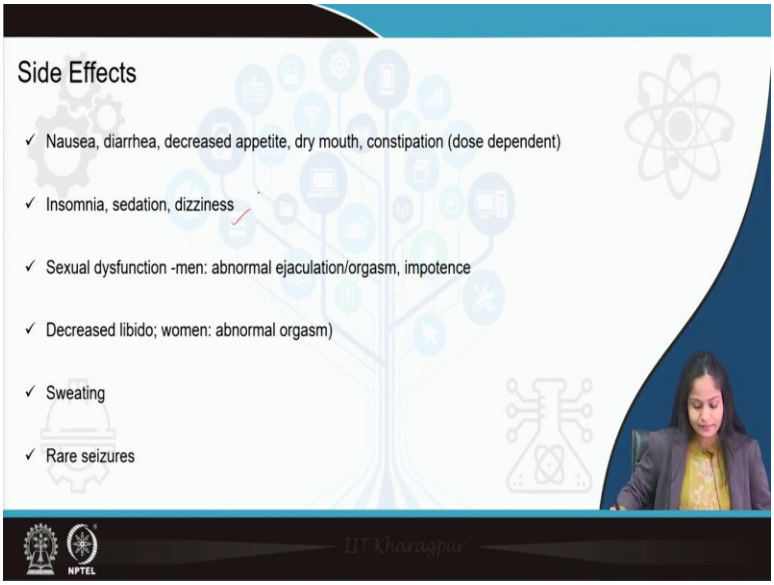

Or again duloxetine is another drug, which is serotonin noradrenergic reuptake inhibitor SNRI, which is used for major depressive disorder, diabetic peripheral neuropathic pain, which is a chronic pain, fibromyalgia, chronic musculoskeletal pain and maintenance for the general anxiety disorder.

So the side effects are again, nausea, diarrhea, the gastrointestinal side effects, that is decreased appetite, those dependent constipation dry mouth, it happens because of the what dose add how much dose you are giving to the person, insomnia, sedation, dizziness, the sexual dysfunction,

which occurs mainly in the main causing abnormal delayed ejaculation importancy decreased libido, both in case of male and females, sweating and rare seizures.

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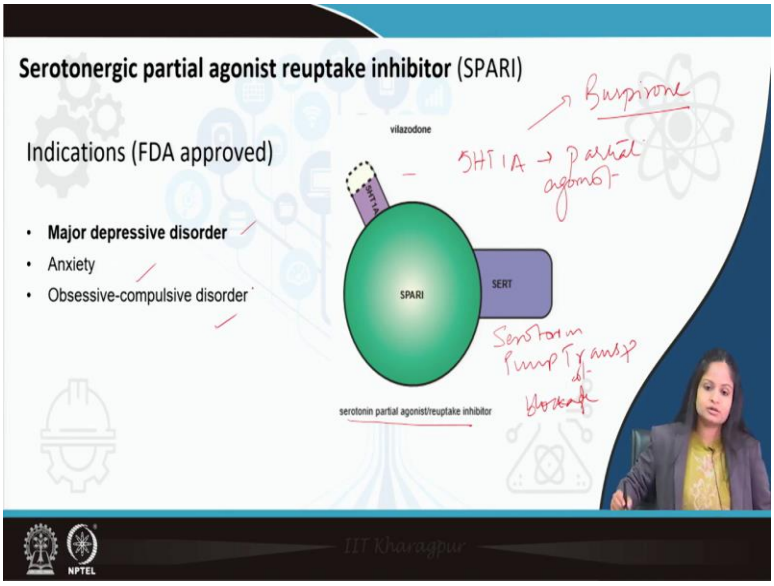

We have the next drug that is SPARI, SPARI is as per the name suggests, it is a serotonin partial agonist and reuptake inhibitors. It is the first action is the serotonin reuptake inhibitor, that is serotonin pump transport blockade. And the second action is 5HT1A partial agonist. The 5HT1A partial agonist if you could remember the partial agonist of 5HT1A is also one of the anxiety drug that is buspirone.

So this drug that is while as you do not or it is SPARI, this is partial agonist of 5HT1A receptor and a blockade of serotonin pump transporter or serotonin reuptake inhibitor so the indications of this drug is major depressive disorder, anxiety and OCD or obsessive compulsive disorder.

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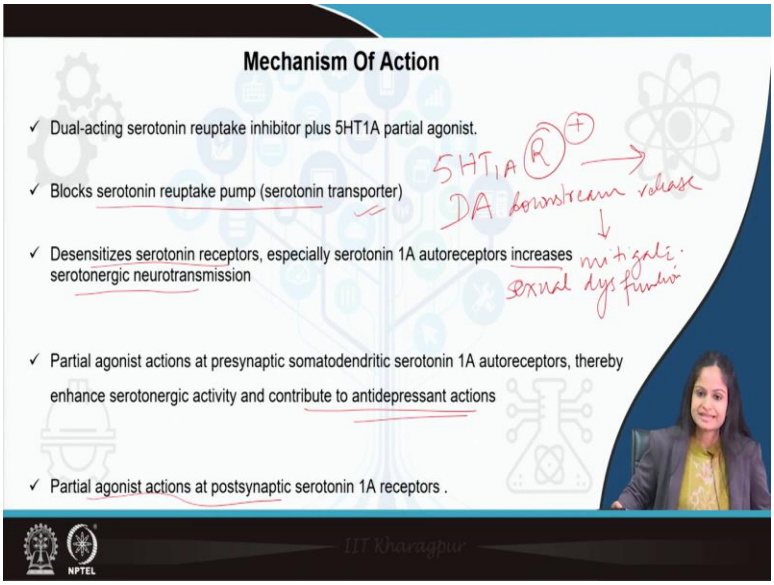

The mechanism of action of SPARI is do well because it is partial agonist of 5HT1 receptor as well as serotonin pump transporter blockade. So it blocks the serotonin reuptake pump or serotonin transporter. So whenever this SPARI is administered to a person what happens half of the serotonin reuptake serotonin pump transporters are blocked and half of the 5HT1 receptors are also blocked immediately.

Now with this blockage, what will happen? There will be serotonin transporters which are blocked and desensitization of the serotonin receptors will occur. So the desensitization of serotonin receptors will finally cause increase in the serotonin level and there will be serotonergic neurotransmission.

So, the somatodendritic level when the serotonin level is increased, so there will be increased in the serotonergic neurotransmission because of the turning on the impulse, this serotonergic neurotransmission finally attributes to the anti depressant actions, but along with that we have the partial agonist actions of 5HT1A receptors.

So, this partial agonistic actions both at pre synaptic level as well as post synaptic level, this will cause the downstream release of dopamine, the 5HT1A receptors, it is a partial agonistic action. So, this will cause downstream release of dopamine. So, with the downstream release of dopamine here the sexual dysfunctions will get decreased. So, it will mitigate the sexual dysfunction or the side effects which are occurring.

So, the sexual dysfunctions or the sexual side effects will get decreased because of the downstream release of the dopamine which is caused because of the pre synaptic and post synaptic activity at the 5HT1A receptors. So, this is the mechanism of action of SPPARI.

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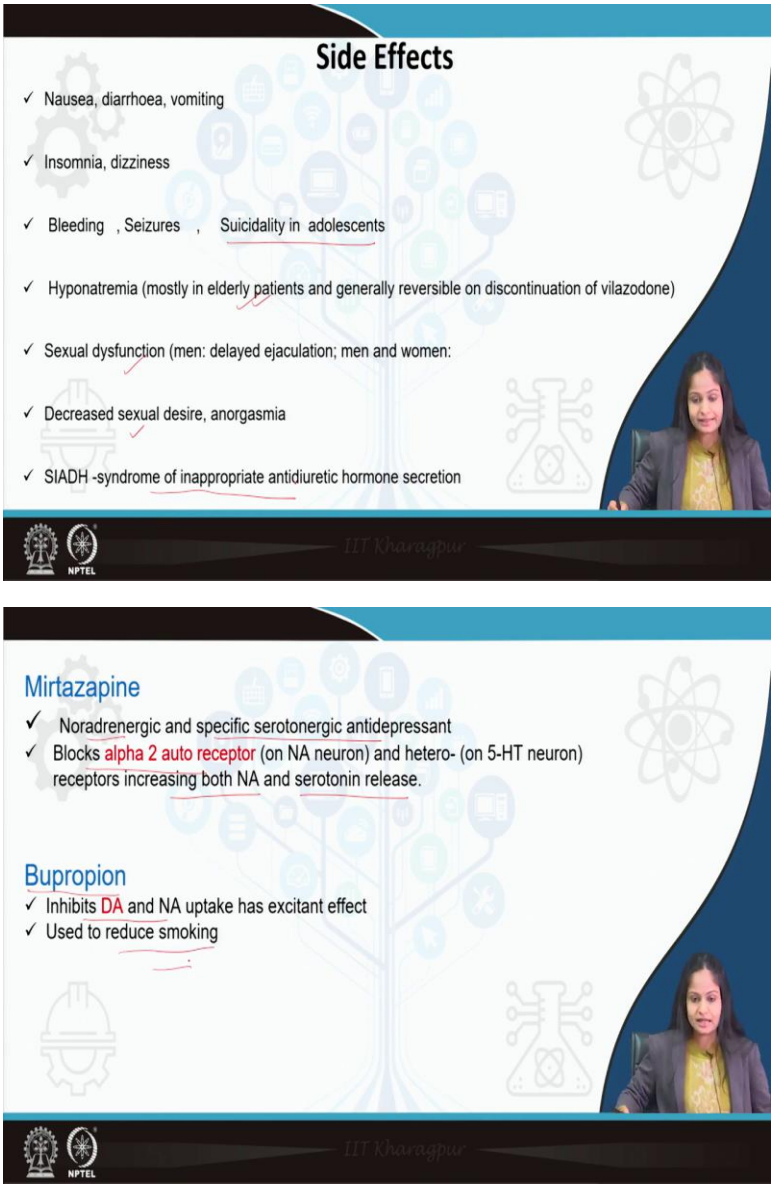

We have the gastrointestinal side effects, that is nausea, vomiting, diarrhea, insomnia, dizziness, there, there is rare conditions of bleeding, seizures, and adolescent suicidality. There is hyponatremia which is also seen in elderly patients which is again reversible which stopped the drug. Then there is decreased sexual desire, decreased sexual desire like anorgasmia that is loss of libido.

And there is syndrome of that inappropriate antidiuretic SAADH that is hormonal secretions. We have two important drugs, that is Mirtazapine and Bupropion these are typical antidepressants which are used the Mirtazapine has noradrenergic and specific serotonergic antidepressants. It has also got an action at the level of alpha 2 auto receptors in blocks the alpha 2 auto receptors and because of this there is release of norepinephrine and serotonin.

This is mainly done by the Mirtazapine. The next drug is the Bupropion, Bupropion inhibits dopamine as well as norepinephrine. So it is usually used to reduce the smoking. So this can be asked as a multiple choice questions. So we have Mirtazapine and Bupropion.

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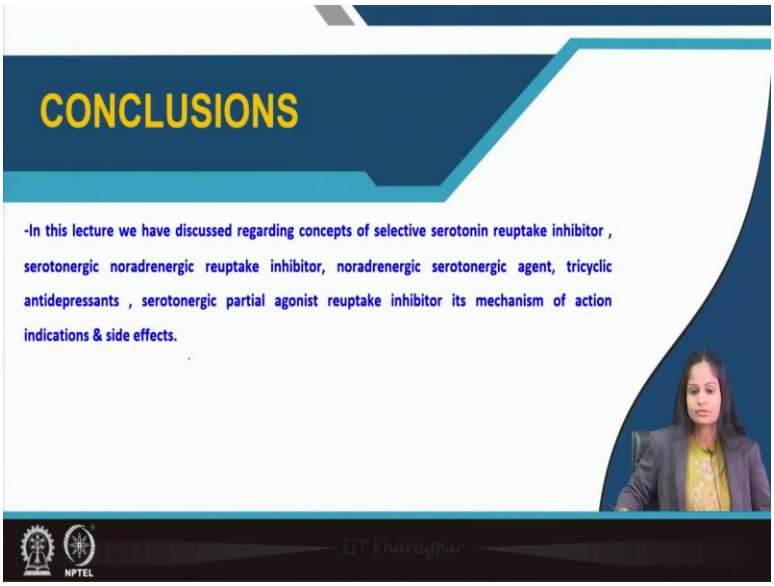

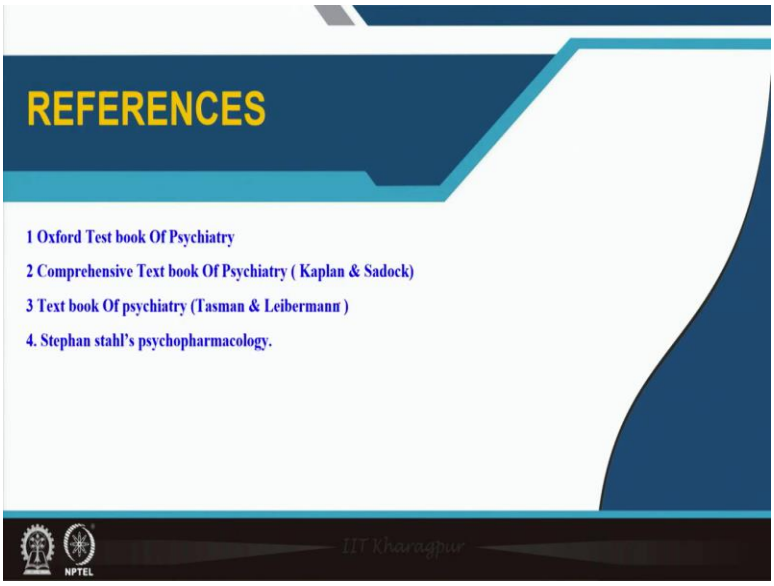

So, in this lecture, we have discussed regarding the activity of monoamine oxidase inhibitors and why these drugs are not used nowadays. Then we had discussed the tri cyclic antidepressants the mechanism of actions of try cyclic antidepressants, the serotonin reuptake inhibitors and its mechanism of actions, the serotonin noradrenergic reuptake inhibitors and the mechanism of actions and the partial agonist, reuptake inhibitors, SPARI and few other atypical antidepressants that is Mirtazapine and Bupropion. So with this, we conclude our lecture. Thank you.