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: 36
Anti-Psychotic Drugs

Hello everyone. So, today we shall start our next topic that is Anti-Psychotic Drugs.

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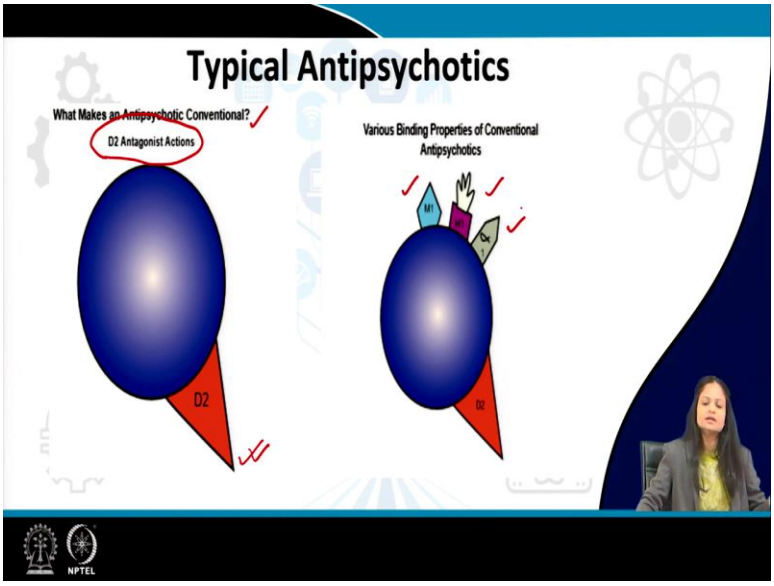

And in this topic, we shall cover the major spectrum of antipsychotic drugs that is typical antipsychotic drugs and atypical antipsychotic drugs. Now, antipsychotic drugs have been a major drive in psychological, psychiatric and neurological research for the past 50 years. And so, we classify antipsychotic drugs majorly into the two broad classification that is typical antipsychotics, as well as atypical antipsychotics.

Now, typical antipsychotics also known as conventional antipsychotics. So, what makes an antipsychotic conventional or typical will go with the typical antipsychotics first. So, what makes an antipsychotic conventional the typicality of an antipsychotic is mainly the D2 or the dopamine two receptor antagonistic actions.

As you can see in the diagram, the D2 are the dopamine two receptor antagonistic actions is the primary pharmacological action which is done by a conventional or typical antipsychotic drug,

the because of this primary pharmacological actions of D2 antagonism, we get its effects as well as the side effects both we get because of this action.

Now, besides this, there are also other binding properties of typical antipsychotics or conventional antipsychotics like it also binds to the M1 receptor, H1 receptor and alpha 1 adrenergic receptors. So, the drugs block the muscarinic receptor, histamine receptor as well as alpha 1 adrenergic receptor.

So, the binding properties of conventional antipsychotics are blocking of the muscarinic cholinergic receptors is histamine receptors as well as alpha adrenergic receptors. So, because of the blocking of these receptors also we get side effects accordingly, but the primary pharmacological function is because of the dopamine receptor blocking action.

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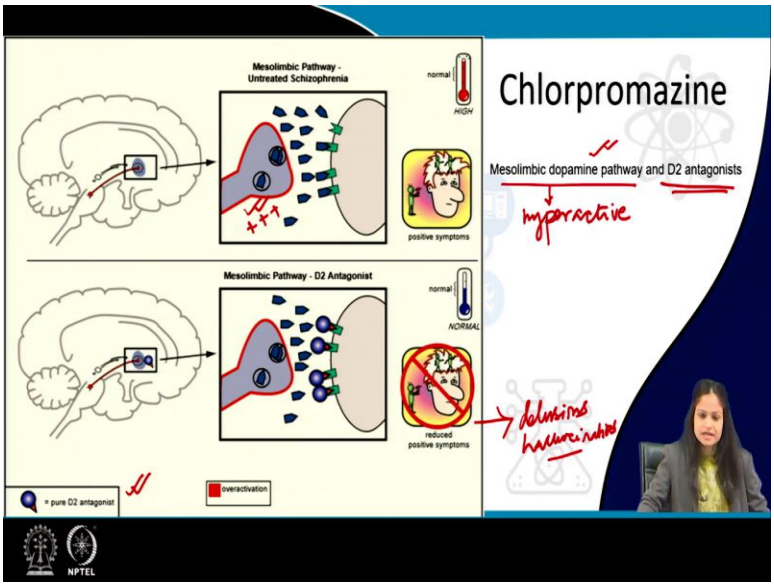

Now, we have various conventional antipsychotics, what you have to remember from exam point of view mainly two antipsychotics, which are conventional that is chlorpromazine and haloperidol. So, the mechanism of actions is general what we will discuss now, besides we have their indications, which are typical for this to drugs.

So, antipsychotic drugs which are typical, what happens in case of untreated psychotic disorder, for example, Schizophrenia, the mesolimbic dopamine pathway set to be overactive or hyperactive active. Now, when this mesolimbic dopamine pathway is hyper active. As you can

see in the diagram, this pathway is hyperactive means it will secrete more and more dopamine in the synapse. So, excess dopamine is secreted in the synapse, and that will result in its effects. So, more than dopamine more is the psychosis.

So, this mesolimbic dopamine pathway is hyperactive in case of untreated psychotic disorders. So, if we want to decrease this action of dopamine, so, we have to use an antagonist, that is dopamine receptor antagonist. So, this dopamine receptor antagonist mainly acting on the D2 receptor will block the dopamine from binding to its receptors and thus that will reduce the positive symptoms.

Now, the positive symptoms are mainly because of the excess dopamine that is mainly the delusions and hallucinations. So, this delusions and hallucinations these are the positive symptoms which occur mainly in the psychotic disorder. So, these positive symptoms are reduced because of this D2 antagonistic actions.

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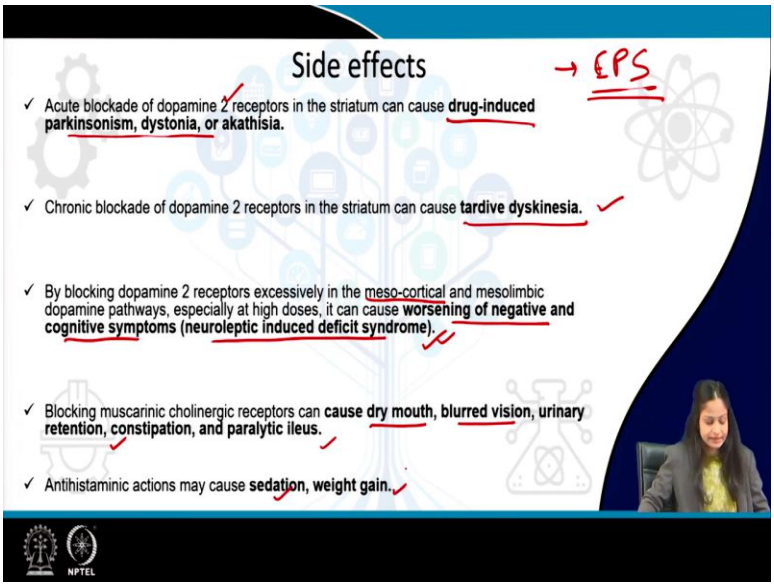

Now, the side effects of these drugs as I told you, because of the same pharmacological actions of the D2 antagonism, now, if this dopamine receptor is blocked in the nigrostriatal pathway, you must be aware by now what is this nigrostriatal pathway this is in the basal ganglia and the dopamine is the key neurotransmitter of this nigrostriatal pathway.

So if any disturbance occurs because of this neurotransmitter in this nigrostriatal pathway that will result in parkinsonism disease, it has already been discussed in basal ganglia lecture. So, I am blocking I am giving our blocker of dopamine that is dopamine receptor blocker. So, obviously this dopamine receptor blockade will occur in nigrostriatal pathway also.

So, that will give rise to the extrapyramidal symptoms that will give rise to extrapyramidal symptoms and the person will be having Parkinsonism like disease, or we call it as drug induced Parkinsonism. So, we can see acute blockage of dopamine 2 receptors in the striatum cause drug induced Parkinsonism there will be extrapyramidal symptoms of dystonia and akathisia.

Now, if the drug is given for a prolonged period, so there will be long term chronic blockage of this receptors that will give rise to tardive dyskinesia. Now, tardive dyskinesia area is also a form of extrapyramidal symptoms or lesions which occurs in the striatum because of the blockage of this dopamine 2 receptors mainly involving the facial muscles and tongue.

What will happen there will be movement disorders of the pay facial muscles and tongue there will be continuous protrusion of the tongue there will be repeated replacing of the pieces there will be continuous chewing and like there is no food in the mouth till the person will keep on chewing so and protruding the tongue.

So this is tardive dyskinesia. If the extrapyramidal symptoms are severe, that can result in muscular rigidity, along with extreme muscular rigidity, along with high fever, coma and death that is known as neuroleptic neromalignant syndrome. So neuromalignant syndrome and neuro lapses are different neuromalignant syndrome is mainly the extreme muscular rigidity, along with high fever and coma.

The second thing is neuro lapses or neuroleptic, induced deficit syndrome. Now, one pathway we know that is mesolimbic pathway dopaminergic pathway. The other pathway is mesocortical pathway. So the mesocortical pathway, this forms the common pathway final common pathway for the actions in the where is leads to the prefrontal cortex.

And hence it is the center for reward, it is attributed this pathway is attributed to reward phenomenon and reinforcement phenomenon, the pleasure orgasm sexual functions eating

feeding behavior. So, if I block this dopaminergic meso cortical pathway or if I am using this drug, antipsychotic drug, which is a dopamine receptor blocker.

So, all these functions will also get lost the person will have no feelings, no emotions, there will be apathy, there will be Anhedonia there will be loss of interest in the activity, there will be sexual dysfunction. So, all the negative symptoms will appear.

So, in a person where the concentration of dopamine is already low, and I am further giving D2 receptor antagonist, so, what I am doing, I will worsen the situations I will worsen the negative symptoms, I will further cause aggravating the negative symptoms. So, that is actually worsening of negative and cognitive symptoms neuroleptic induced deficit syndrome and as I had already told you.

Because of the blocking of the histamine receptors as well as muscarinic cholinergic receptors and alpha adrenergic receptors, subsequent side effects will be there like cholinergic receptors block it will cause dry mouth blurred vision, urinary retention, constipation and paralytic ileus. Whereas, on the other hand antihistaminic x that will lead to sedation and mainly weight gain.

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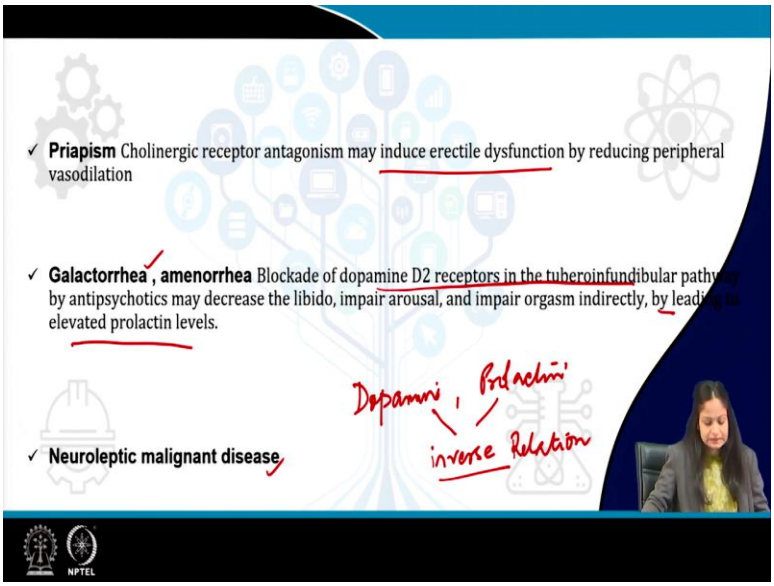

Then we have priapism, priapism is painful erection. So, the cholinergic receptor antagonism which we are using that may cause erectile dysfunction or painful erections, this usually occurs

because of the reduction of the peripheral blood flow or the reduction, reducing peripheral vasodilation.

Then we have galactorrhea amenorrhea now, and Neuroleptic Malignant disease which already I had discussed, now dopamine and prolactin levels, dopamine and prolactin. These two they are they form an inverse relationship or the reciprocal relationship that means whenever there will be more dopamine so there will be less prolactin, whenever there will be less dopamine so there will be more prolactin.

So I am here using a blockade the drug is a blockade of dopamine receptors so obviously there will be less dopamine. So that will indirectly cause the prolactin level to get increase so that is why the person will have elevated prolactin levels. And as the same way, the D2 receptors will get blocked in the tuberoinfundibular pathway causing various sexual dysfunctions and decrease in the libido and impair arousal. So, these are the mainly side effects of the drugs.

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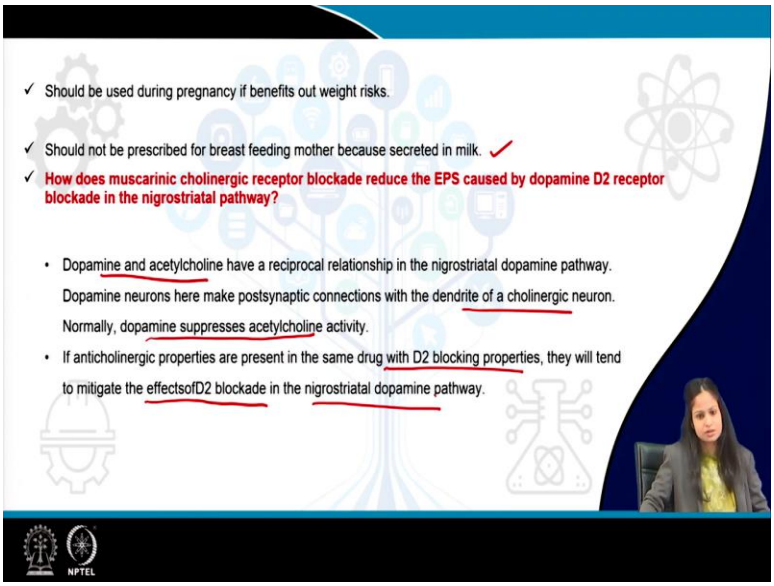

Besides this the question arises whether this drug could be used during pregnancy or not, it should be used during pregnancy provided the benefits are more than the side effects you have to weigh the benefits and then you have to use the drug and definitely should not be prescribed during in the lactating mothers or the breastfeeding mothers because the drug is secreted in the milk. So it should not be used or prescribed for the lactating mothers.

Now, is there any way we can decrease this extrapyramidal symptoms? Yes, if you are using any drug which is possessing the cholinergic anticholinergic activity also that is muscarinic cholinergic receptor blockade activity also, or simultaneously along with D2 receptor blockade I am using any anticholinergic drug muscarinic receptor blockade.

Then this extrapyramidal symptoms could get reduced. So how is it happening now dopamine and acetylcholine. These also have a reciprocal relationship in the nigrostriatal pathway. If you could remember the basal ganglia lecture there, I have shown you that the dopamine neurons, they make a postsynaptic connections with the dendrite of the acetylcholine or the cholinergic neuron. So, what will happen usually the dopamine suppresses the acetylcholine activity, whenever the dopamine actions will be there, the acetylcholine activity will get suppressed.

So, if anticholinergic properties are present in the same drug. Where this D2 blocking properties are there, or subsequently we are simultaneously with the D2 blockade receptor, due to blocking agent we are using any muscarinic receptor blockade and that will tend to decrease the effects of D2 blockade in the Nigrostriatal dopamine pathway and it would give certain relief to the extrapyramidal symptoms occur in the person.

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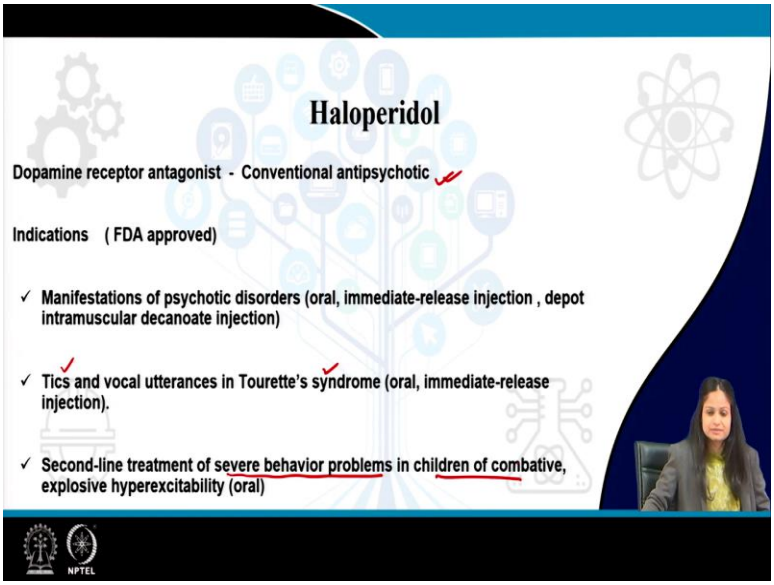

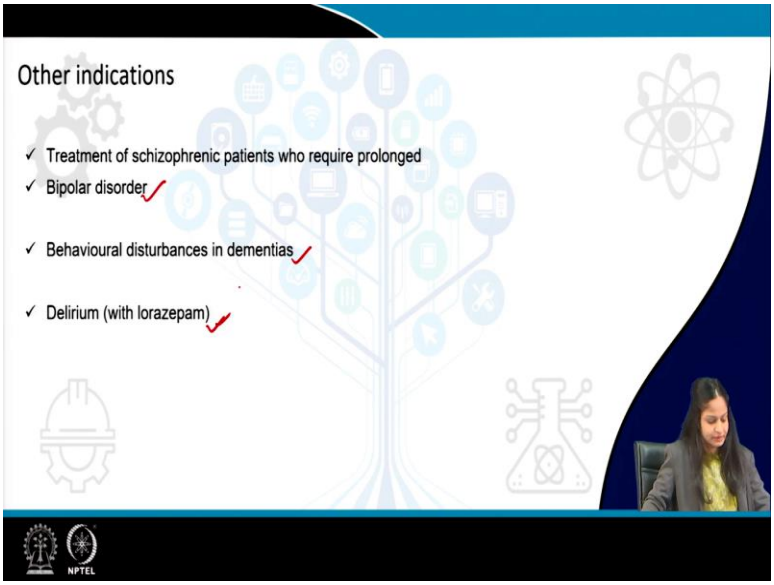

So, these are the features of the chlorpromazine drugs and haloperidol drug is also the same, may opposite the same mechanism of action that is of the conventional antipsychotic. The indications of haloperidol is the manifestations of psychotic disorders it is given both in injectable form as well as orally.

It is also used in tics and tourette's syndrome, then it is a second line treatment for severe behavioral disorders in children who are very much explosive or hyperexcitable in nature. So and other indications also of haloperidol are the bipolar disorder, behavioral disorders or behavioral

disturbances in dementias. And if the person is having delirium, then we can give haloperidol along with a benzodiazepine that is Lorazepam.

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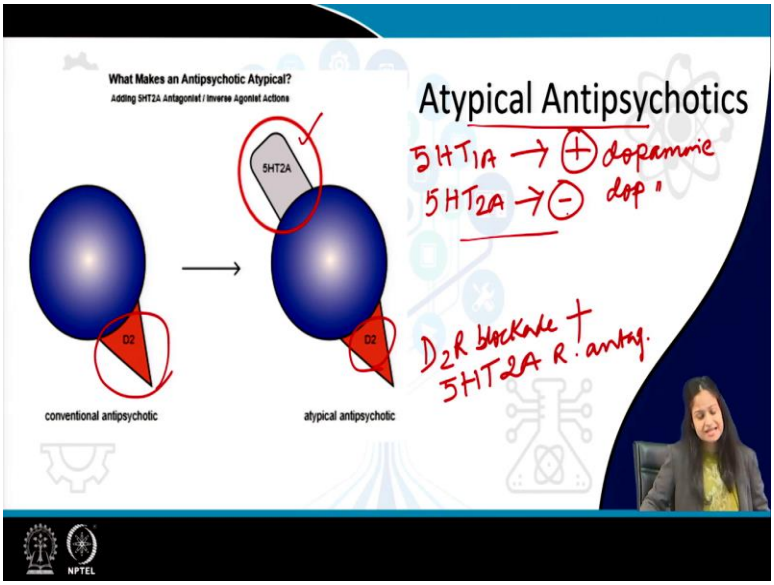

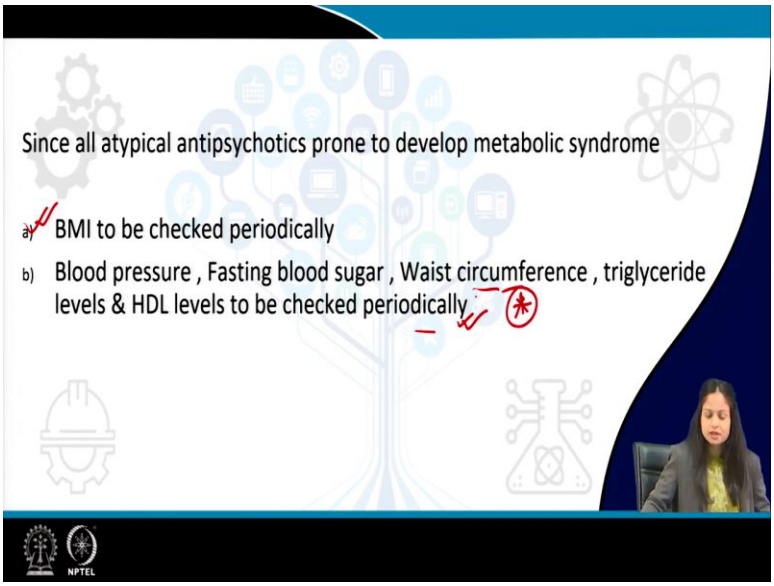

Now, coming to the use of or coming to the mechanism of actions of atypical antipsychotics. Till now, we have discussed about the typical antipsychotics. So, what makes an antipsychotic atypical, now, typicality was because of the D2 blockade dopamine receptor blockade atypicality is because of the 5HT2A antagonism along with dopamine receptor blockade.

So, these two antagonism will occur at the same time, there will be D2 receptor blockade or antagonism as well as 5HT2A receptor antagonism. Now, a very important thing to be remembered is 5HT1A, this causes increase in the dopamine release. This will cause increase in the dopamine release, whereas, 5HT2A this causes inhibition in the dopamine release.

How this will cause inhibition in the dopamine release is it actually in your decreases of dopamine release due to the GABAenergic actions, the glutamate release will be enhanced with the help of this receptor. And because of this glutamate release, it will cause the it will stimulate the GABA to get released on the dopaminergic neurons and GABA will inhibit the dopamine to get released.

So 5HT2A in inhibit the dopamine release and 5HT1A stimulate the dopamine release this you, you have to remember. Now in case of atypical antipsychotic usually, besides several side effects, the main side effect is the metabolic syndrome, there is increase in the weight, obesity, insulin resistance, dyslipidemia, and finally results in the metabolic syndrome.

So, the BMI should be checked periodically (in this patient) in the subject, as well as checking regularly the blood pressure fasting blood sugar level, the triglycerides level, the cholesterol level, the waist circumference level, these are to be checked periodically because these are very important, the person usually goes to the metabolic syndrome.

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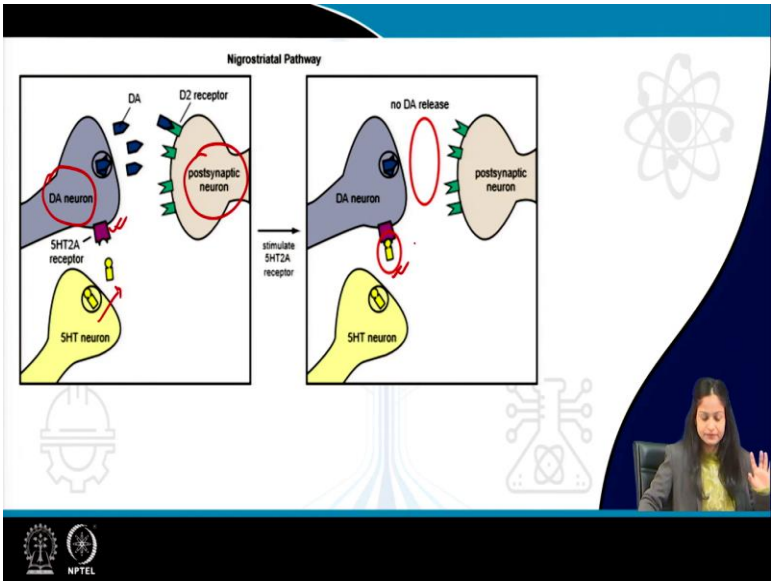

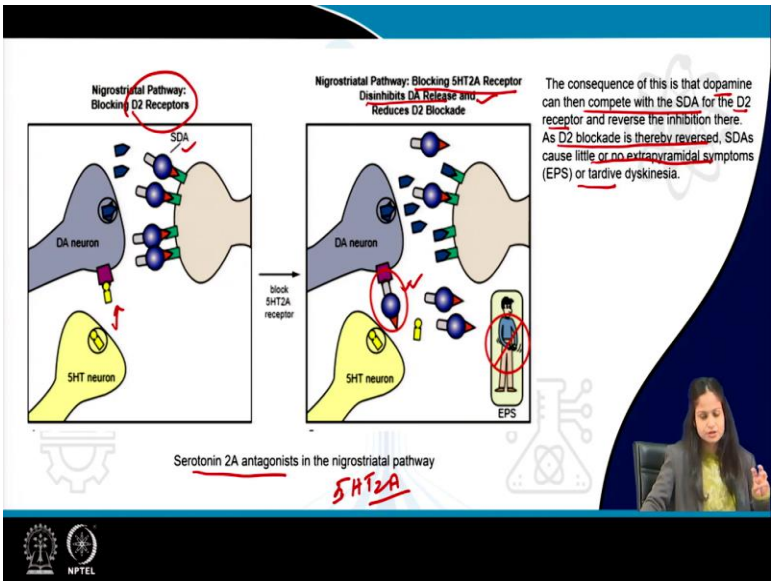

Now, what mechanism of action it causes that will see? So, this is an eyebrow striatal pathway. Here we can see this is the dopaminergic neuron, which is bearing the 5HT2A receptor, the 5HT2A receptor is secreting this serotonin. Now before the binding of serotonin, the dopamine receptors are present in the postsynaptic neuron.

Now dopamine will get released and dopamine will bind to its receptor. Now, if there is stimulation of the 5HT2A receptor, how it will get stimulated whenever the serotonin will get bind to the receptor. So whenever there will be binding of the serotonin to this receptor, that dopamine neuron that will inhibit the dopamine release the inhibition I told you that is mainly via glutamate and GABA release mechanism, the GABA will inhibit the dopamine release.

So, the 5HT2A receptors whenever it gets stimulated by binding of the serotonin to the receptor, dopamine will not get released and this is the normal phenomenon. So, now, what we are using we are using the D2 receptor blockade along with the 5HT2A receptor antagonism. So, initially the typical antipsychotics when we are blocking the D2 receptors, we can see there is no blockage of the receptors.

So, serotonin is getting released and here and it is binding to the receptor as well as dopamine whichever is getting released, that dopamine is also getting blocked by the receptors the because of the dopamine blocking of the receptor. So, what will happen if we are using serotonin, serotonin 2A antagonist that is 5HT2A antagonism, what will happen that will whenever the serotonin release will be blocked by this antagonism.

The inhibition of the dopamine release will get this inhibited this is known as this inhibition of the dopamine release. So, you can see blocking of the 5HT2A receptor these inhibits dopamine release and reduces the D2 blockade that means, when I am blocking 5HT2A receptor, what does it do it decreases the dopamine release. So, I am blocking that.

So, I am blocking that, that is antagonistic property. So, whenever there is a blocking of the serotonin receptor what will happen, so, there will be dopamine release. So, the consequence of this is dopamine can compete with the serotonin antagonist for the D2 receptor and reverses the inhibition that means there will be this inhibition of the dopamine release and as D2 blockade is there by reversed.

So, this will cause no or little because the, there will be little extrapyramidal symptoms because the dopamine is now available at the synaptic junctions to get attached to the receptors. So, in this way extrapyramidal symptoms are decreased. Now, the main purpose of discovery of this typical antipsychotics was to lessen the side effects. And the major side effects which were done by the conventional antipsychotics are the extrapyramidal symptoms. So in this way the extrapyramidal symptoms are reduced.

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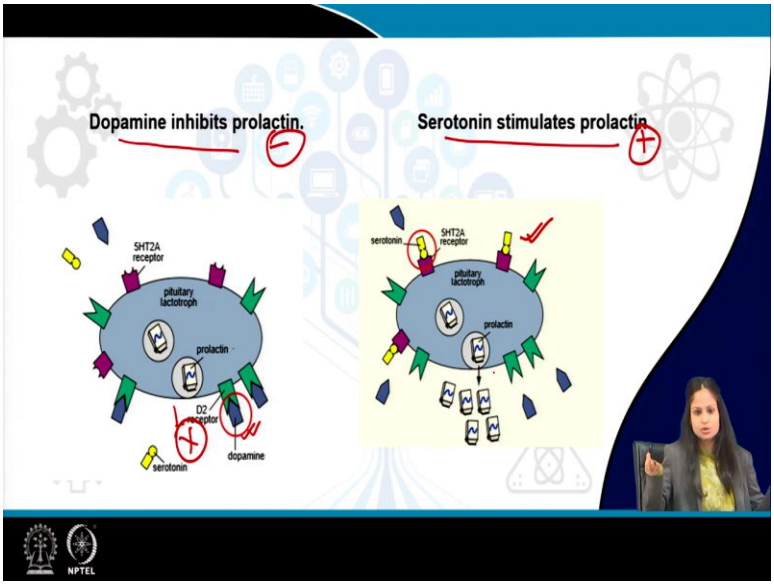

And also we could reduce the galactorrhea as it has been shown, I told you that dopamine and prolactin has got an inverse relationship. Now, what you have to remember is when dopamine is binding to the receptor is dopamine receptor, the prolactin is not getting released. Because

dopamine is inhibiting the prolactin release from the pituitary lactotrops. But serotonin causes stimulation of the prolactin release.

When serotonin is binding to the receptors, 5HT2A receptors there is release of the prolactin so there is an inverse relation, which is going on. On one way, dopamine is inhibiting prolactin on the other way serotonin is stimulating the prolactin release.

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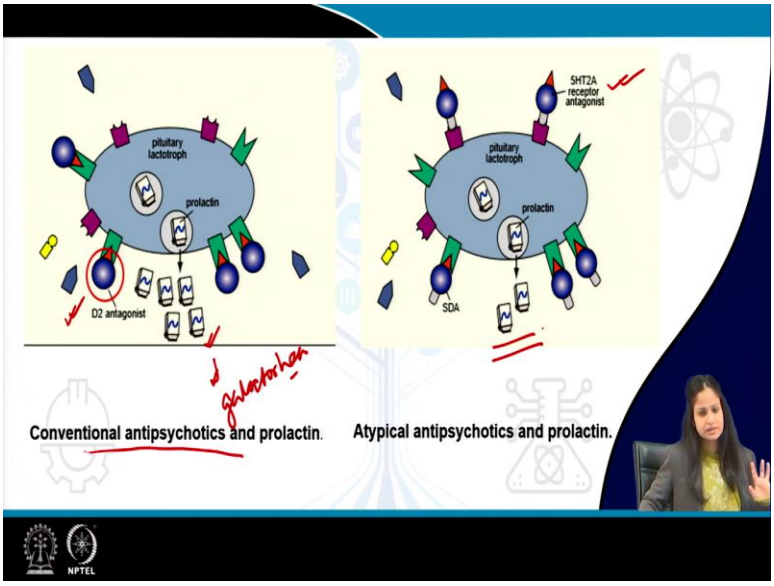

Now, in case of conventional antipsychotics, what happened, as I told you, due to the dopamine 2 receptor blockade, there is less dopamine. So the inverse relationship is applicable over here. So prolactin will be more and this results in the galactorrhea. But in case of atypical antipsychotics, were along with the dopamine receptor blocker. I have this 5HT2A receptor antagonist also. So there will be nullification of this action.

The 5HT2A receptor will tend to nullify the D2 receptor blockade, the D2 receptor blockade will tend to nullify the action of the serotonin receptor antagonist that is 5HT2A receptor blockade. So in this way, finally there will be normal release of the prolactin and there will be not no less release or no more release. So finally there will be normal release of the prolactin from the pituitary lactotrops. In this way galactorrhea is prevented.

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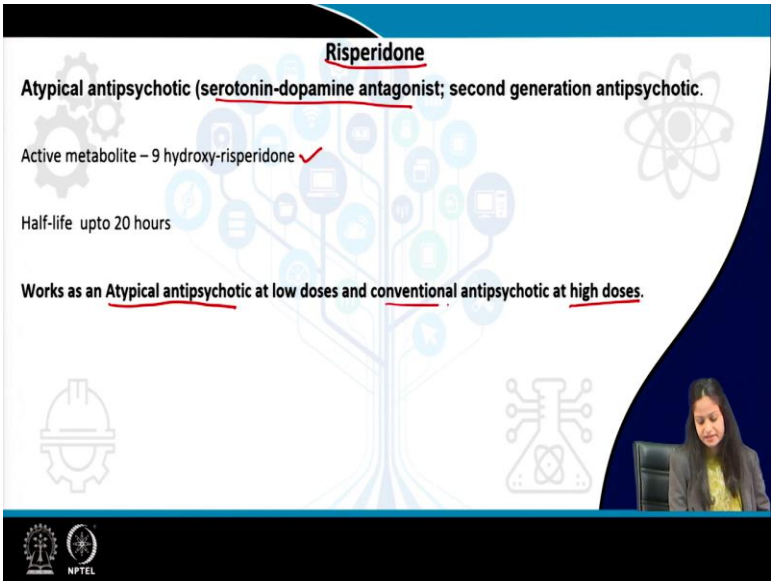

So the various drugs are there in case of atypical antipsychotics. We will discuss few of them. First drug is Risperidone. Risperidone is an atypical antipsychotic, which acts on the serotonin dopamine antagonists. The second generation antipsychotic its active metabolite is 9 hydroxy risperidone. It has gotten half life of 20 hours.

Now at low doses, it acts as a typical antipsychotic at high doses it will act as conventional antipsychotic. So this you have to remember of Risperidone.

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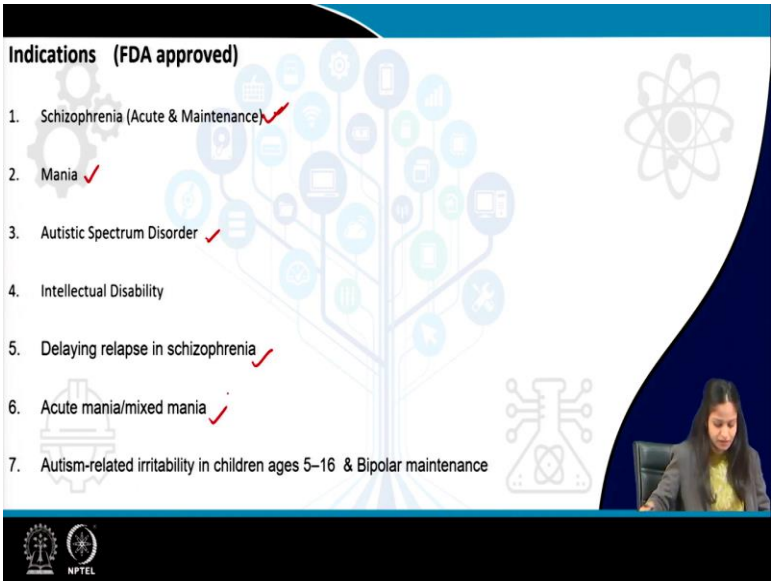

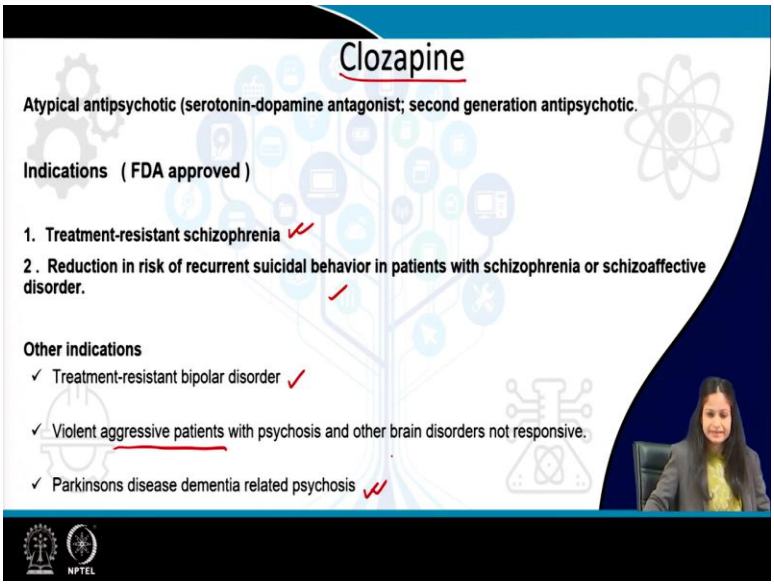

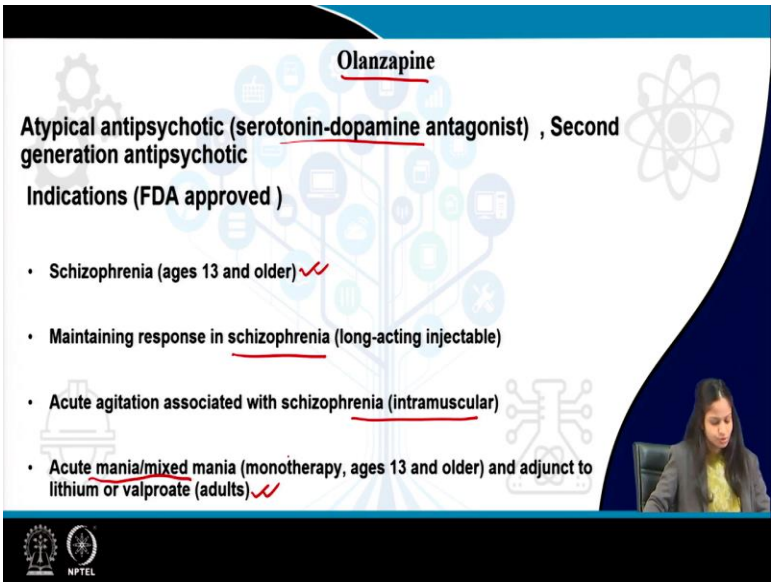

Now, what are the indications of Risperidone were this can be used in case of acute and maintenance therapy of Schizophrenia, Mania, Autistic Spectrum Disorder, Intellectual disability. If I want to delay the relapse phase of Schizophrenia there, acute mania, in case of bipolar maintenance and children where autism is causing irritability, there we can use. The next drug is Clozapine.

Clozapine is also a typical antipsychotic which is bearing the same mechanism of actions that is 5H2A or serotonin dopamine antagonist, the indications are treatment resistant schizophrenia, where we are using the conventional and antipsychotic Schizophrenia treatment has become resistant to that there we can use.

If we want to reduce the suicidal behavior in case of psychotic patients. There we can use the other treatment resistant bipolar disorder whenever there is violent, aggressive patients with psychosis or any brain disorders which are not responsive to the treatment. And in case of Parkinsonism related dementia who are having psychotic features there. Then the next drug is Olanzapine.

Olanzapine is a typical antipsychotic drugs which is also wearing the same mechanism of actions. That is serotonin dopamine antagonist. The indications of this drug is against Schizophrenia which can be used in case of children that is 13 years old and older to that, if I want to maintain long term or maintenance therapy or response in Schizophrenia, then acute agitation associated with schizophrenia.

We can use intramuscular injections of olanzapine in acute agitation of schizophrenia. In acute mania therapy, we can use obviously in adjunct with the lithium or valproate, which is used in adults, the main treatment for the mania. So there we can use olanzapine.

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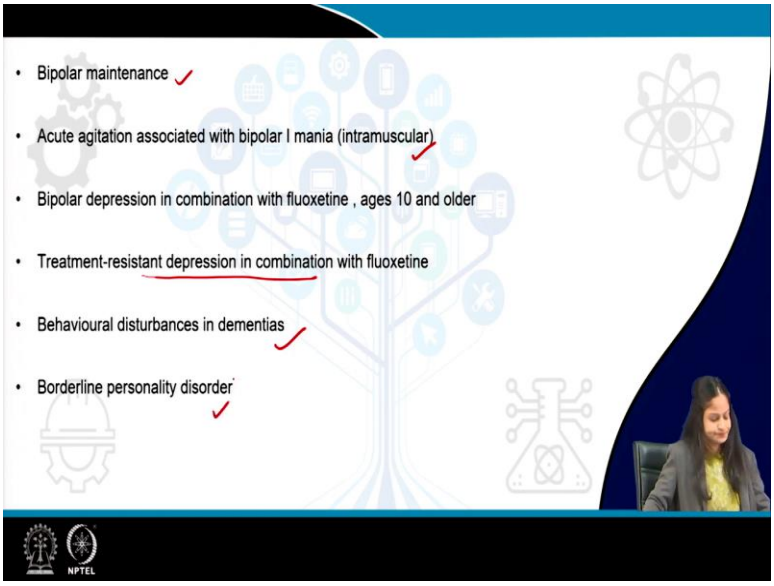

Besides that we can use olanzapine in the bipolar maintenance acute agitations with the bipolar mania, Bipolar depression along with fluoxetine, treatment resistant depression in combinations with fluoxetine, behavioral disturbances and dementia and borderline personality disorder.

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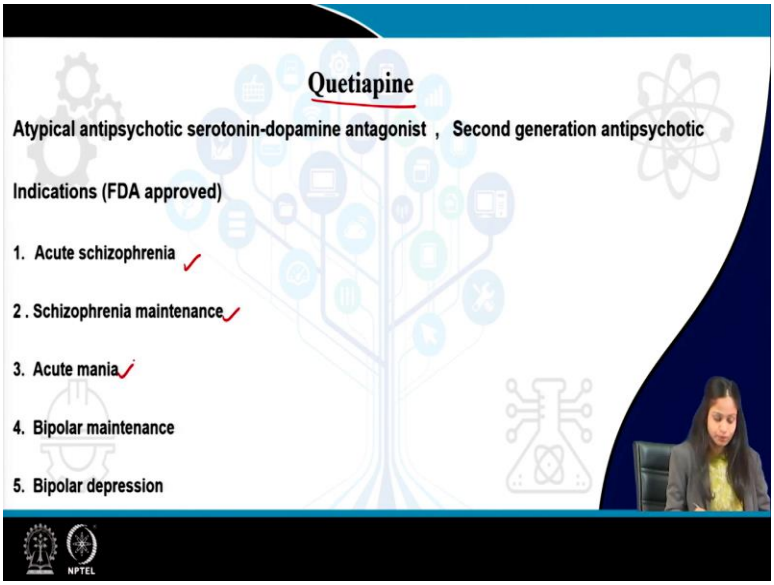

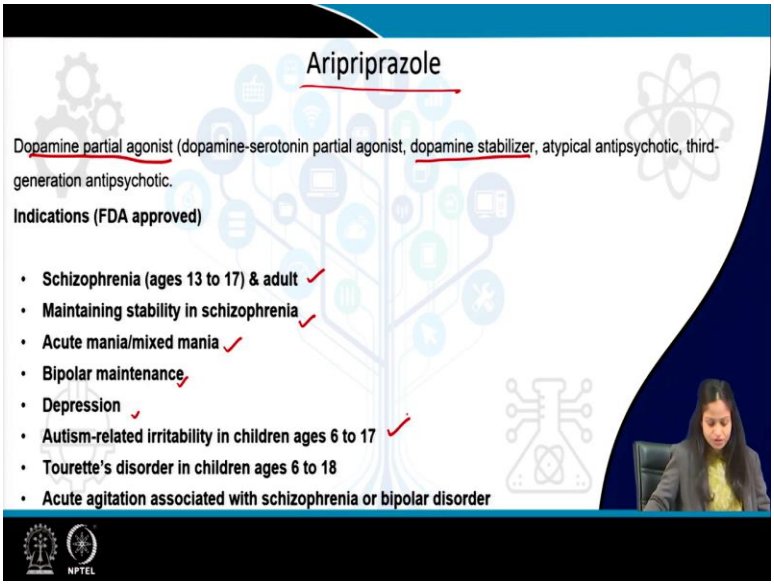

Now, coming to the another drug, that is Quetiapine, these are the drugs which bear till now, these are the drugs which bear the same mechanism of actions that is of serotonin dopamine antagonist. So, this the indications of Quetiapine, Acute schizophrenia, Schizophrenia maintenance, Acute mania, Bipolar maintenance, Bipolar depression.

Now coming to the drug, which bears the mechanism of actions bit different from that of what we had started till now, that is the second generation antipsychotic that is dopamine serotonin receptor antagonist. Now, the name of the drug is Aripriprazole, this Aripriprazole is a dopamine partial agonist.

So what do you mean by a partial agonist, dopamine serotonin partial agonist. Now, excess dopamine will cause psychosis very less dopamine is causing extrapyramidal symptoms. So there a drug should be there, which would cause a balance between this excess dopamine and very less dopamine. So that is neither it neither causes the psychosis nor it causes the extrapyramidal symptoms.

So this is the drug which stabilizes or balances the dopamine the neurotransmitter. And this is a typical antipsychotic drugs, which is a third generation antipsychotic drugs. So it is indications are Schizophrenia in between the age group of 13 and 17, as well as adult, maintaining stability and schizophrenia, acute mania, bipolar maintenance, it is also used in depression, and autism related irritability, the tourette's disorder in children, and acute agitation which is associated with schizophrenia or bipolar disorder.

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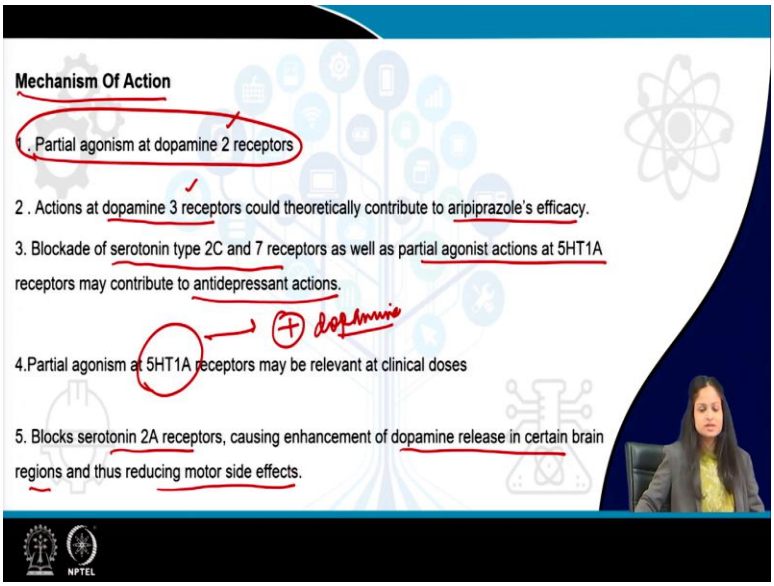

Now the mechanism of actions is very important of this aripiprazole's because the mechanism of actions of this drug is associated with its function, like whether it is called antipsychotic actions, how it will cause anti depressant actions et cetera. Now, the main mechanism of action is the partial, the partial agonism of dopamine 2 receptors this is very important as I already had told you, the partial agonist of dopamine 2 receptors which will stabilize the key neurotransmitter that is dopamine, the actions at the second thing is the actions are dopamine 3 receptor.

So, this is of the dopamine 2 receptor, this is of dopamine 3 receptors. Now, when there is an action of the dopamine 3 receptors theoretically contributes to the aripiprazole's efficacy, and blockade of serotonin type 2C and 7 receptors. So, we have serotonin type 2C and 7 receptors. Now, each receptors are contributing to each specific function of this drug.

So, dopamine 2 receptors stabilizer blockade agonism of partial agonistic of dopamine 2 receptors a stabilizer, dopamine 3 receptor is mainly for the efficacy blocking of the serotonin type 2C and the 7 receptor as well as the partial agonist actions of 5HT1A receptor mainly contribute to the antidepressant actions. Now, this 5HT1A receptors I told you this is actually a stimulatory, plays a very stimulatory role in dopamine release.

So 5HT1A agonistic actions. Again blocking of serotonin 2A receptors this will cause and enhancement of the dopamine release in certain brain regions and that will reduce the motor side effects that is the mainly the extrapyramidal symptoms. So there is a blocking of 2A receptors 5HT1A receptor agonistic actions, agonistic actions of the D2 receptors and blockade of the serotonin type 2C and the 7 receptors.

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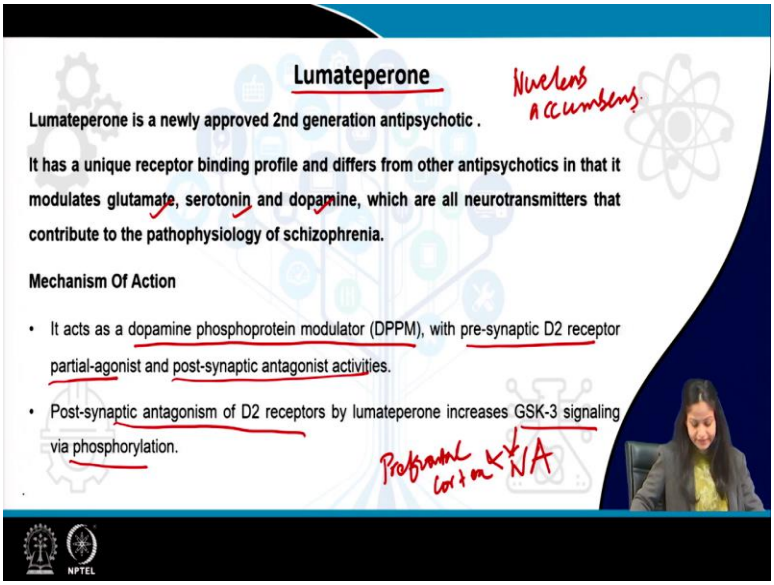

Now coming to the last drug that is a newly approved second generation antipsychotic that is Lumateperone. This Lumateperone has a very unique property as an antipsychotic because it modulates the key 3 neurotransmitters, glutamate, serotonin and dopamine, glutamate, serotonin and dopamine these play a major role in the pathophysiology of schizophrenia.

So now we will see the mechanism of actions again, each the binding of Lumateperone with various receptors that mainly plays the role or contributes to its various actions. So first and foremost, the main important action of this drug is dopamine phosphoprotein modulator. It modulates the phosphorylation so dopamine phosphoprotein modulator.

It acts pre synaptic as an partial agonist, post synaptically acts as an antagonist. So, pre-synaptically it will act D2 receptor as an agonist function. But post synaptically it will act as antagonistic functions. Post synaptic antagonistic functions increases the GSK 3 signaling via phosphorylations, glycogen GSK 3 signaling is glycogen synthase kinase 3 signaling this is very important.

Initially it was attributed to the glucose metabolism in our body and it is very important for the insulin signaling processing in our body various cellular processes related to growth factors metabolism, and now what is various psychiatric disorders attribute to this GSK 3 signaling and this mainly occurs at the prefrontal cortex and nucleus accumbens, nucleus accumbens main site for the addictions site.

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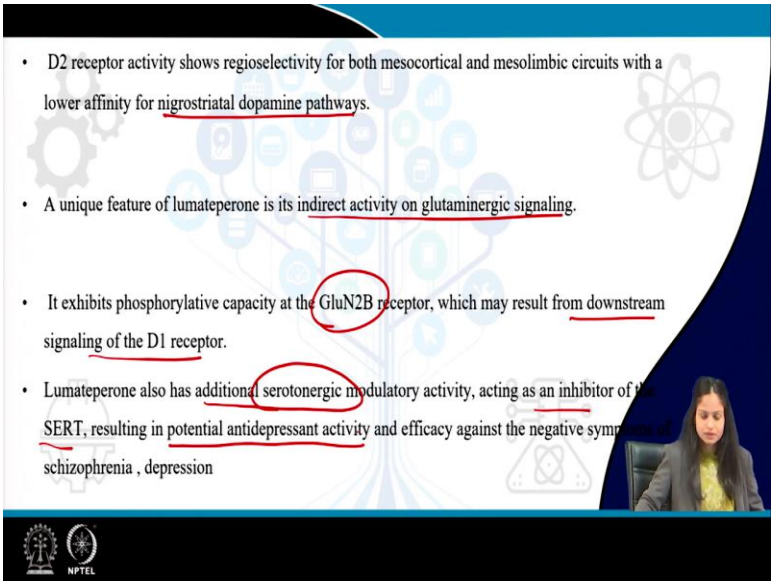

So, besides that D2 receptor activates shows low affinity that is for the nigrostriatal dopamine pathway. A unique feature of this is the indirect activity on the glutamineergic signaling, it exhibits phosphorylative capacity at the GluN2B receptors which causes downstream of the D1 receptor.

And Lumateperone has also got an additional serotonergic modulatory activity, which the serotonergic modulatory activity will cause the inhibitor of the serotonin reuptake transporters. And that will that results in the potential antidepressant activity and efficacy against the various negative symptoms that is a psychotic disorder mainly depressions. So in this way, Lumateperone acts in various ways. It plays a role as an antipsychotic, it plays a role as a potential antidepressant activity, and it causes downstream signaling of the D1 receptors.

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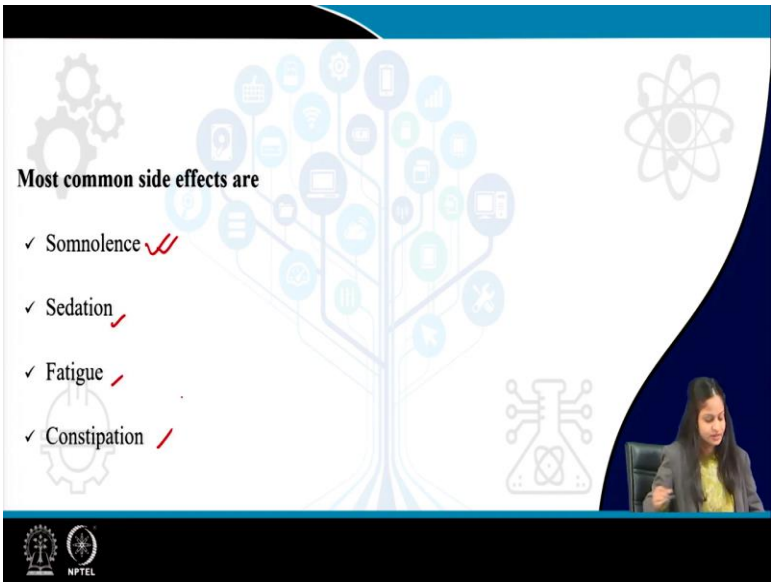

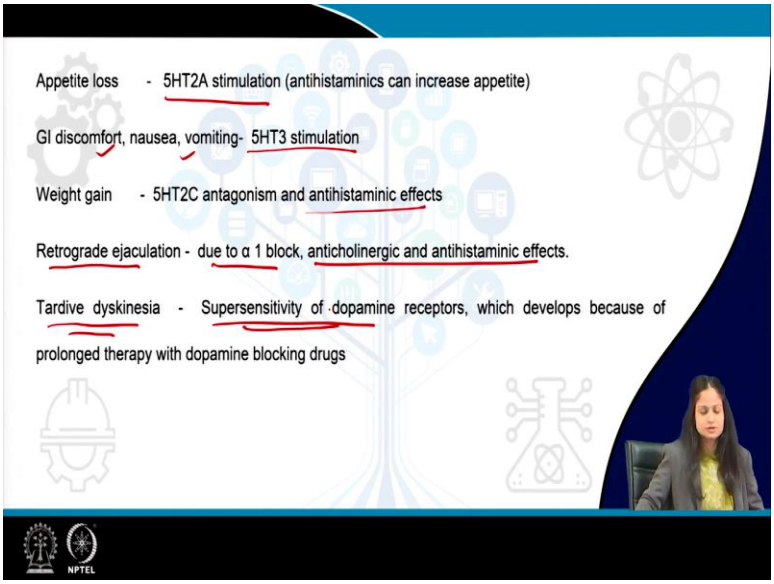

The various side effects includes Somnolence, increased sleepiness, sedation, fatigue, constipation, these are the most common side effects. The other side effects are attributed to

because of the binding of the various receptors like appetite loss is mainly because of the 5HT2A stimulation, mostly the antihistaminic cause increase in the appetite. So if you are stimulating 5HT2A that will cause appetite loss. The GI disturbances nausea vomiting is mainly because of the 5HT3 stimulation.

The weight gain is mainly because of the antihistaminic actions. Retrograde ejaculation is mainly because of the Alpha 1 blockage, anticholinergic and antihistaminic properties mainly because of the Alpha 1 blockage. And Tardive dyskinesia because of the prolonged use or prolonged therapy with the dopaminergic receptor blocking drugs which causes super sensitivity of the dopamine receptors. So that causes tardive dyskinesia.

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So in this lecture, we had discussed the various types of antipsychotics, the conventional typical antipsychotics and its mechanism of actions and the first line of drugs which are used. Then we had discussed the atypical antipsychotics and its mechanism of actions, including the Risperidone, Olanzapine, Quetiapine, Clozapine, Aripriprazole and the mechanism of action of the newly antipsychotic second generation that drug that is Lumateperone. So, thank you.