AN OVERVIEW OF TARDIVE DYSKINESIA

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ABSTRACT

Tardive Dyskinesia (TD) is one of the muscular side effects of anti-psychotic drugs especially the older generation anti-psychotic drugs characterized by "pill-rolling" movements of the fingers, darting and writhing movements of the tongue, lip puckering, facial grimacing, and other irregular movements.. In the present review we discuss about the drugs to treat schizophrenia (typical and atypical) and their side effects like extra pyramidal symptoms (EPS) (acute dystonia, akasthesia, parkinsonism and tardive dyskinesia) and advantage of atypical over typical antipsychotics. In this mainly focus on the tardive dyskinesia, incidence of TD after neuroleptic treatment, classification of tardive dyskinesia, symptoms of TD, diagnosis of TD. Different mechanisms explain how antipsychotic treatment causes TD and pathophysiology physiology of TD. To treat tardive dyskinesia different approaches like prevention of TD by supplying anti oxidants and vitamins, and for the treatment reduction of dose of anti psychotics and different drugs are discussed here.

Keywords: TD, Extra Pyramidal, Dystonia, Akasthesia, Cognitive.

INTRODUCTION

Tardive Dyskinesia (TD) is one of the muscular side effects of anti-psychotic drugs especially the older generation anti-psychotic drugs. TD occurs after many months or years of antipsychotic therapy. Older anti psychotics exhibit potential side effects like akathisia (restlessness), dystonia (sudden and painful muscle stiffness) and Parkinsonism (tremors and slowing down of all body muscles). TD is characterized by random movements of tongue, lips or jaw as well as facial grimacing, movements of arms, legs, fingers and toes, or even swaying movements of the trunk or hips and which disappear during sleep. [1]

Neuropsychiatric Disorders and Importance Of Drug Therapy

Schizophrenia is one of the most complex and challenging of psychiatric disorders. It has been conceptualized as a disorder characterised by the familiar positive (hallucinations, delusions, bizarre behaviour, positive formal thought disorder and inappropriate affect) and negative (affective flattening/ blunting, alogia, avolition/apathy, anhedonia/asociality, inattention) groups of symptoms.[8]

In schizophrenia there is increase in dopamine content in the regions of brain such as Substantia nigra innervated in Caudate nucleus Putamen (these are highly innervated by dopamine neurons. These neurons originate mainly from the substantia nigra pars compacta (SNc). Responsible for the Extrapyramidal system, movement disorders.

Ventral tegmentum (these are group of neurons located close to the midline on the floor of the midbrain (mesencephalon). The VTA, the origin of dopaminergic cell bodies that comprise the mesocorticolimbic dopamine system, innervated in limbic areas of amygdala, olfactory tubercle, septal nuclei, and cingulate gyrus. Responsible for the Arousal, memory, stimulus processing, motivational behavior.

Midbrain ventral tegmentum innervated in Frontal and prefrontal lobe cortex responsible for Cognition, communication, social function, response to stress.

Hypothalamus and Pituitary gland Regulates prolactin release.

The decrease in glutamate NMDA (N-methyl-D-aspertate) receptor also produces psychosis.

Table 1: Symptoms of schizophrenia

Type	Effect	Note
Positive Symptoms	- Delusions - Hallucinations - Thought disorder	Symptoms which are more responsive to antipsychotic medication than negative symptoms.
Negative Symptoms	- Flat affect -Poverty of thought - Amotivation -Social withdrawal	Develop with progression of illness, cause disability, persistence signifies onset of chronic illness.
Cognitive	- distractibility - Impaired working memory - Impaired executive function	Dysfunction tends to occur in association with negative symptoms.
Mood	- Mania - Depression	Mood disorder often occurs in schizophrenia. Anxiety can occur at any stage of illness.

Table 2: Drugs used and frequency of common side effects of antipsychotics[2]

S.No	Drug	Sedation	Extrapyramidal	Postural hypotension	Anticholi-nergic	Weight gain
Typical drugs						
1	Chlorpromazine	↑↑↑	↑↑	↑↑↑	↑↑↑	↑↑↑
2	Droperidol	↑↑	↑↑↑	↑	↑	↑
3	Fluphenazine	↑	↑↑↑	↑	↑	↑↑↑
4	Haloperidol	↑	↑↑↑	↑	↑	↑↑
5	Pericyazine	↑↑↑	↑	↑↑	↑↑↑	↑↑
6	Pimozide	↑↑	↑↑↑	↑	↑	↑
7	Thioridazine	↑↑↑	↑	↑↑↑	↑↑↑	↑↑↑
8	Trifluoperazine	↑	↑↑↑	↑↑	↑	↑↑
9	Zuclopenthixol acetate	↑↑↑	↑↑↑	↑	↑↑	↑↑
10	Zuclopenthixol Dihydrochloride	↑↑↑	↑↑↑	↑	↑↑	↑↑
Atypical drugs						
1	Amisulpride	↑	↑↑*	↑	0	↑
2	Aripiprazole	↑↑	↑	↑	0	↑
3	Clozapine	↑↑↑	↑↑	↑↑↑	↑↑↑	↑↑↑
4	Olanzapine	↑↑↑	↑	↑	↑↑	↑↑↑
5	Quetiapine	↑↑↑	* ↑	↑↑	↑	↑↑
6	Risperidone	↑↑	↑↑	↑↑↑	0	↑↑
7	Ziprasidone	↑↑	↑	↑	↑	↑

Approximate frequencies of adverse effects:
0 (<2%) = negligible or absent;
↑ (>2%) infrequent;
↑↑ (>10%) = moderately frequent;
↑↑↑ (>30%) = frequent
* rarely a problem at usual therapeutic doses

Difference between typical and atypical anti psychotics:
All antipsychotics have affinity to D_2 receptors of mesolimbic and nigrostriatal pathways. But atypical antipsychotics have more affinity to mesolimbic and less affinity towards nigrostriatal D2 receptors. [3] Typical antipsychotic drugs alleviate positive symptoms but not all; typical antipsychotic drugs have little effect on the negative symptoms of schizophrenia. Atypical antipsychotic drugs are effective against positive symptoms and significantly more effective against negative symptoms than that of typical antipsychotic drugs in patients with schizophrenia. There is also

considerable evidence favoring atypical antipsychotic drugs against both depressive symptoms and cognitive impairment.[8]

Side effects of antipsychotic drugs:

The side effects commonly seen with conventional antipsychotics include sedation, anticholinergic effects, extrapyramidal symptoms (EPS), orthostatic hypotension, weight gain, photosensitivity, and elevated prolactin levels. Sedation and the feeling of tiredness are very common with all antipsychotics.[3]

Extra pyramidal symptoms (EPS) are neurological disturbances caused by antipsychotics in the area of the brain that controls motor coordination. The antipsychotics drug can produce symptoms like Parkinson's disease. They cause Parkinson like symptoms (parkinsonism) that include muscle stiffness, rigidity, tremor, drooling, and a "masklike" face.[3]

Table 3: Extra pyramidal movement disorders associated with antipsychotic agents[4]

S.No	Disorder	Typical onset	Features
1	Acute *Dystonia*	First few doses	*Dystonic reactions (painful spasm of a muscle or muscle group)* Oculogyric crisis - fixed upward stare Torticollis - neck twisting Trismus - clenched jaw Opsithotonus - arching of the back Laryngospasm – difficulty breathing, speaking or swallowing.
2	Akathesia	with few week of treatment	*Subjective feeling of inner restlessness, anxiety and motor restlessness* Inability to sit still, constant pacing Continuous agitation and restless movements Rocking and shifting of weight while standing Shifting of legs, tapping of feet while sitting.
3	Parkinsonism	With few months of treatment	*Rigidity and immobility* Stiffness and slowness of treatment voluntary movement Mask-like facial expression Drooling Stooped posture Shuffling, festinating gait Slow, monotone speech. *Tremor* Regular rhythmic oscillations of the extremities, especially the hands and feet Pill-rolling movement of the fi ngers.
4	Tardive Dyskinesia	After at least six months of treatment	*Mouth* Rhythmical involuntary movements of the tongue, lips, jaw Protrusion of the tongue, puckering of the mouth, chewing movements. *Choreiform* Involuntary irregular purposeless quick movements of arms/legs Jerky, flailing movements. *Athetoid* Continuous wormlike slow movements of arms. *Axial hyperkinesis* To and fro clonic movements of the spine.

Dystonia is a type of EPS with acute onset. It is manifested by a sudden spasm of muscles involving the tongue, jaw, and neck. This is not an allergic reaction to the antipsychotic medication. Although a dystonic reaction may be painful and frightening, it can be rapidly reversed with an intramuscular injection of an anticholinergic medication, such as benztropine or diphenhydramine. With a dystonic reaction, the patient should seek immediate medical attention and receive treatment.

Akathisia is another form of EPS characterized as a subjective sense of restlessness accompanied by fidgeting, inability to sit still, nervousness, muscle discomfort, and agitation. Use of propranolol , a beta-blocker, may be helpful.

Elevation of prolactin levels[3] is common with conventional antipsychotics. Prolactin is a hormone produced in the area of the brain called the pituitary gland. It is normally elevated in women following childbirth, stimulating lactation, or milk production. The elevation of prolactin caused by antipsychotic

medications may cause breast enlargement and milk production (galactorrhea) in both women and men. Elevated prolactin is also associated with impotence in men and irregular or absence of menstruation in women. When side effects from elevated prolactin levels affect the patient, the alternative is to switch to one of the second-generation antipsychotic agents, which do not elevate prolactin.

Weight gain is a frequent side effect of all antipsychotic medications. Certain antipsychotics are associated with greater weight gain than others. It is unclear whether this is due to an underlying metabolic change caused by the antipsychotic or to increased appetite. Weight should be monitored closely during therapy, and if weight gain occurs, an intervention program of diet and exercise should be started.[3]

When antipsychotics interfere with the action of cholinergic neurons in the nervous system, they produce bothersome anticholinergic side effects. When an organ system is affected by cholinergic inhibition, it causes side effects particular to that organ. For example, when the gastrointestinal tract is affected, dry mouth, cramping and constipation result. Other anticholinergic side effects include blurred vision (when muscles of the eyes are affected) and difficulty urinating (when the bladder is affected). The low-potency first-generation antipsychotics have more anticholinergic activity than the high-potency agents. When antipsychotics are combined with other medications with significant anticholinergic activity.[3]

Tardive Dyskinesia

Tardive dyskinesia is a potential adverse reaction from antipsychotic medications. It is a late-onset abnormal involuntary movement disorder. It is a potentially irreversible condition with symptoms that commonly include "pill-rolling" movements of the fingers, darting and writhing movements of the tongue, lip puckering, facial grimacing, and other irregular movements. The risk of TD is increased the longer the person has been taking the antipsychotic and this risk also increases with age. With several decades of experience, scientists now have a better understanding of the relative risk of TD with conventional antipsychotics than with the second-generation antipsychotics. However, because the second generation antipsychotics have a very low incidence of EPS, these newer antipsychotics may also have very low risk of inducing TD.

CLASSIFICATION OF TARDIVE DYSKINESIA [5]

Tardive dyskinesia can be classified as a syndrome that can be divided into separate clinical subtypes:

1. Classical Tardive Dyskinesia
2. Tardive Dystonia
3. Tardive Tic
4. Tardive Akathisia
5. Withdrawal Emergent Syndrome

Patients may present with one or more of these subclasses.

Classical Tardive Dyskinesia[5]

Classical tardive dyskinesia is characterized by involuntary lip smacking and pursing, movement of the tongue side-to-side (bon-bon sign), tongue protrusion (Fly-catcher's tongue), chewing movements, respiratory dyskinesia (diaphragm and intercostal involvement), pelvic thrusting, choreiform limb movements, tapping and side-to-side foot movements, and marching in place. The dyskinesia appears to affect the lower face more than the upper face. It has been suggested that these movements can be further classified into central and peripheral syndromes. Central movements are composed of the orofacial dyskinesia, whereas the peripheral movements include those of the limb and axial muscles. The classification into these two syndromes is justified by their different clinical course. Central movements progress over many years, while peripheral movements remain constant and show little change in their severity.

Tardive Dystonia[5]

Tardive dystonia due to neuroleptic therapy is similar to idiopathic torsion dystonia. However, unlike the idiopathic form, patients may present with other drug-induced movement disorders, including classical orolingual buccal TD, tardive akathisia, or myoclonus. Tardive Dystonia occurs equally in the children and adults. However, younger patients show a more generalized involvement, while adults demonstrate a focal or segmental involvement.

Tardive Tic[5]

Tardive tic may develop in a small number of patients on chronic neuroleptic therapy, which resemble Gilles de la Tourette syndrome (make repeated and uncontrolled (involuntary) movements and sounds (vocalizations) called tics.). These patients demonstrate spontaneous vocal and motor tics. These include barking, clicking, grunting and verbalization.

Tardive Akathisia[5]

Tardive akathisia is described as a subjective restlessness or need to move, which may occur early in the course of Neuroleptic therapy. Some of the stereotyped motor movements attributed to TD, including repetitive touching of the forehead and scalp, crossing and uncrossing of legs, pacing and body rocking, may be due to akathisia.

1) Can't sit still

2) Inner feeling of restlessness/anxiety/discomfort

3) Restlessness usually more severe when trying to fall asleep

4) Compulsion to keep moving

5) Itchy, painful burning tingling skin

6) Depression that never existed before

7) Suicidal thoughts/actions which never existed before

Withdrawal Emergent Syndrome

Withdrawal emergent syndrome is common in children who develop involuntary movements after cessation of long-term Neuroleptic therapy. This is considered the least serious of the tardive syndromes since it is self-limiting and disappears within 6 - 12 weeks. [5]

Incidence of TD [1, 6, 7]

Essentially, prolonged exposure to antipsychotic treatment is the major reason that TD occurs in an individual. Some persons get it sooner than others. The risk factors that increase the chances of developing TD are

a) Duration of exposure to antipsychotics (especially the older generation),

b) Older age,

c) Postmenopausal females,

d) Alcoholism and substance abuse,

e) Mental retardation and

f) Experiencing a lot of EPS in the acute stage of antipsychotic therapy.

SYMPTOMS

TD is characterized by involuntary, repetitive, purposeless movements that vary in localization and form and occur on, jaw, lips, face, trunk, upper extremities, lower extremities, and respiratory system.[14] The main symptoms of TD are continuous and random muscular movements in the tongue, mouth and face, but sometimes the limbs and trunks are affected as well. Rarely, the respiration muscles may be affected resulting in grunts and even breathing difficulties. Sometimes, the legs can be so severely affected that walking becomes difficult. [6,7]

Table 4: symptoms of tardive dyskinesia

Symptoms	Symptoms	Symptoms
Tongue moves in mouth	blowing/puffing/burping/unintended noises/clicking	Hands cramped (difficulty grasping\holding)
Tongue protrudes out of mouth	Difficulty breathing (diaphragm)	Arms/hands shake
Chewing	Different (muscle tension or “hatband”) headaches	Toes move
Teeth grinding	Jaw ache/tension/spasm	Feet cramp
Difficulty swallowing	Head pulls to one side	Difficulty walking
Difficulty eating	Unusual dental problems	Back twisting or arching
Difficulty speaking	Biting inside of mouth\tongue	Stomach movements
Facial grimacing	Drooling	Hip gyrating
Puckering	Slurred speech\thick tongue	Diaphragm uncontrolled causing grunting and unusual noises
Blinking	Arms move	Unusual feeling of rapid heartbeat\anxiety
Eyes pull to one side	Legs move (like restless leg syndrome, but not)	Tremulousness
Excessively frequent eye movements	Fingers move	Bouncy legs
Repeated forehead wrinkling	Hands drawn up	

DIAGNOSIS OF TARDIVE DYSKINESIA:

Physical examination

Abnormal involuntary movement scale (AIMS) is designed to measure involuntary movements known as tardive dyskinesia (TD).[9]

Procedure:

The AIMS examination procedure will be done for each patient those are in Psychotropic medication. The examination procedure should also be done at any time believe that a patient may be displaying increased symptoms of Tardive Dyskinesia. The entire test can be completed in about 10 minutes. The AIMS test has a total of twelve items rating involuntary movements of various areas of the patient's body. These items are rated on a five-point scale of severity from 0–4. The scale is rated from 0 (none), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe). Two of the 12 items refer to dental care.[10]

Instructions:
Movement ratings:
Rate highest severity observed.
Rate movements that occur upon activation
One less than those observed spontaneously

CODES:
0 = none, 1 = Minimal, may be extreme, normal, 2 = Mild, 3 = Moderate, 4 = Severe.

Table 5: AIMS Scale

Area	Effect	Circle One				
Facial and oral movements	Muscles of Facial Expression e.g., Movements of forehead, eyebrows, periorbital area, cheeks, include frowning, blinking, smiling, grimacing	0	1	2	3	4
	Lips and Perioral Area e.g., puckering, pouting, smacking	0	1	2	3	4
	3. Jaws e.g., biting, clenching, chewing, mouth opening, lateral movement	0	1	2	3	4
	4. Tongue Rate only increase in movement both in and out of mouth, NOT inability to sustain movement	0	1	2	3	4
Extremity Movements	5. Upper (arms, wrists, hands, fingers) Include choreic movements (i.e., rapid objectively, purposeless, irregular spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine) Do NOT include tremor (i.e., repetitive, regular, rhythmic)	0	1	2	3	4
	6. Lower (legs, knees, ankles, toes) e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0	1	2	3	4
Trunk Movements	7. Back, shoulders, hips e.g., rocking, twisting, squirming, pelvic gyrations	0	1	2	3	4
Global Judgments	8. Severity of abnormal movements	0	1	2	3	4
	9. Incapacitation due to abnormal movements	0	1	2	3	4
	10. Patient's awareness of abnormal movements *RATE ONLY PATIENT'S REPORT*	No Awareness .....0 Aware, Mild distress .....2 Aware, No distress .....1 Aware, Severe distress 4				
Dental Status	11. Current problems with teeth and/or dentures	No.....0 Yes 1				
	12. Does patient usually wear dentures?	No.....0 Yes 1				

A rating of 2 or higher on the AIMS scale is evidence of tardive dyskinesia. If the patient has mild TD in two areas or moderate movements in one area, then he or she should be given a diagnosis of TD. The AIMS test is considered extremely reliable when it is given by experienced raters. [11]

Laboratory studies

Laboratory studies include history and physical examination, past history of brain lesions, a family history, presence of dementia or signs of other neurologic, metabolic, endocrine abnormalities.

Laboratory studies include

A. Complete blood count- to rule out polycythemia vera and other disorders.

B. Serum electrolytes- to omit abnormalities of sodium and calcium metabolism that may cause movement disorders.

C. Liver function test- know the other causes of liver dysfunction.

D. Thyroid function test- to check possible hyperthyroidism.

E. Serum copper and ceruloplasmin and urinary copper and amino acid in case of suspected wilson's disease.

F. Connective tissue disease screen- to assess for systemic lupus erythematous and other vasculitides.

Mechanisms of Antipsychotic Induction of TD

Many mechanisms have been proposed to explain how antipsychotics induce TD. The most accurate theory was postsynaptic dopamine receptor hypersensitivity. This

model explains how long-standing blockade of dopamine in the nigrostriatal pathway receptors leads to permanent receptor hypersensitivity. And damage to striatal GABA-containing neurons, damage or degeneration of striatal cholinergic interneurons and production of excessive free radicals and oxidative stress will induce tardive dyskinesia.[12]

a. Postsynaptic dopamine receptor hypersensitivity

All antipsychotics drugs both typical and atypical block the dopamine D2 receptors. Many non-antipsychotic medications that block dopamine have also been associated with TD. Increasing in dopaminergic receptor blockade suppresses tardive dyskinesia. After long-standing EPS later TD will be development.PET (Positron emission tomography) data show that D2 binding is increased after long-term antipsychotic treatment in humans. [(37)] (The degree of D2 upregulation likely corresponds to the propensity for TD to develop.)

b. Damage to striatal GABA-containing neurons

Decreased activity of glutamic acid decarboxylase in the substantia nigra, globus pallidus, and subthalamic nucleus produce oral movements after induction of neuroleptics. Decreased number of striatal neurons after long-term antipsychotic treatment. Antipsychotic-induced degeneration of striatal-pallidal or striatal-nigral GABA-aminergic pathways, or both.[12]

c. Damage or degeneration of striatal cholinergic interneurons caused by prolonged overactivation of striatal cholinergic neurons when released from dopaminergic inhibition after antipsychotics is administered.

d. Prolonged blockade of postsynaptic dopamine receptors.

Increased dopamine formation after long term antipsychotic treatment leads to the free radical metabolites formation. Increased excitatory glutaminergic transmission from prefrontal cortex to striatum.

PATHOPHYSIOLOGY:

Dopamine Hypersensitivity

Dopamine hypersensitivity theory has approaches to studying TD. It proposes that the nigrostriatal dopamine system develops increased sensitivity to dopamine as a consequence of chronic dopamine receptor blockade induced by neuroleptic drugs.[15, 16]

Neurotoxicity

Another hypothesis is that TD is due to neurotoxic effects of free radical by products from catecholamine metabolism. The basal ganglia, by virtue of their high oxidative metabolism, would be particularly vulnerable to membrane lipid peroxidation as a result of the increased catecholamine turnover induced by neuroleptic drugs.

GABA Insufficiency

Another competing hypothesis involves gamma-aminobutyric acid (GABA) insufficiency in the neuroanatomical loop controlling movement.

Other Neurochemical Hypotheses

Because most neuroleptics also antagonize many other receptor types besides dopamine, it is possible that these play an important role in the pathophysiology of TD. A noradrenergic dysfunction theory derives some support from findings of greater dopamine β-hydroxylase activity in TD patients compared to non-TD patients

Serotonin may modulate dopamine activity and thus be involved with TD. However, efforts to find consistent abnormalities of serotonin parameters or effective serotonin treatments for TD offer little support for this hypothesis. Cholinergic hypo function has been proposed as a cause of TD.

GENETIC SUSCEPTIBILITY TO TARDIVE DYSKINESIA

Genetic factors may cause some people to be more susceptible to developing tardive dyskinesia than others. Genetic polymorphisms coding for dopamine receptors may explain differences in susceptibility to tardive dyskinesia. Genetic polymorphisms for dopamine receptors may impact dopamine binding affinity, which would potentially make some patients on neuroleptic medications more susceptible to tardive dyskinesia than others.

Metabolizing CYP450 polymorphs like CYP3A4*1B and CYP2D6*4 polymorphisms in TD susceptibility among chronic schizophrenia patients. [18]

Tardive dyskinesia was diagnosed in ~29% of the patients. No significant association of either of the two SNPs (single nucleotide polymorphism) with TD (CYP3A4*1B; CYP2D6*4) was observed. [18]

ANIMAL MODELS FOR TARDIVE DYSKINESIA

Rat models of tardive dyskinesia:

Neuroleptic-induced perioral movements in rat described enhancement of oral behavior result from chronic administration of chlorpromazine, trifluoperazine, or thoridazine were treated for 12 months in drinking water exhibited incidence of spontaneous mouth movements while stereotypy response to apomorphine was inhibited.

High intensity components blocked by neuroleptics whereas the low intensity component, which is not blocked, is responsible for the enhanced chewing behavior. It was demonstrated that, rats treated with haloperidol that manifested vacuous chewing behavior exhibited reduced GAD activity and GABA levels in substantia nigra, Globus pallidus, and hypothalamic nucleus.

Treatment of rats with fluphenazine decanoate for a six or nine months period results in the manifestation of vacuous chewing behavior. [21]

Animals:

Male Sprague dawley rats weighing 250-300gm were used for all studies. Rats were housed four to a case in an animal facility at 21±1^{o} C with a relative humidity of 555% under a 12h dark-light cycle and with free access to commercial food pellets and tap water.

Behavioral assessment:

On the test day, rats were placed individually in a small (30 × 20 × 30 cm) Plexiglas cage for the assessment of oral dyskinesia. Animals were allowed 10 min to get used to the observation cage before behavioral assessments. To quantify the occurrence of oral dyskinesia, hand-operated counters were employed to score tongue protrusion and vacuous chewing frequencies. In the present study, VCMs are referred to as single mouth openings in the vertical plane not directed toward physical material. If tongue protrusion or VCMs occurred during a period of grooming, they were not taken into account. Counting was stopped whenever the rat began grooming, and restarted when grooming stopped. Mirrors were placed under the floor and behind the back wall of the cage to permit observation of oral dyskinesia when the animal was faced away from the observer. The behavioral parameters of oral dyskinesia were measured continuously for a period of 5 min. In all the experiments, the scorer was unaware of the treatment given to the animals.[22]

Monkey model of tardive dyskinesia:

Long term treatment of cebus paella monkey with haloperidol or flupenazine induced symptoms of TD that persist for a long period of time after withdrawal.

Tardive dyskinesia in monkeys represents a valid model which in many ways can serve as a replication of this syndrome in humans. Although there have been no entirely satisfactory model of abnormal involuntary dyskinetic movements of orofacial area following neuroleptic treatment the monkey model appears to be closely related to the clinical symptomology in humans. The use of animal models often provides an insight into human pathology and into drug induced side effects that can't be acquired by other means and or of particular value in the search for effective treatment.

Prolonged administration of haloperidol or chlorpromazine to cebus paella monkey result in abnormal oral behavior. After three and six months of treatment, two of these monkeys developed bucco-lingual movements, grimacing and tongue protrusion that were pronounced before each dose of activity and GABA levels in substantia nigra, medial Globus pallidus, and subthalamic mucleus relative to control monkeys.

Prevention of tardive dyskinesia:

TD can be prevented by early recognition and discontinuation of the antipsychotic medication or reduction in dosage is the first approach. Nonetheless, the difference between symptoms remaining permanent or going away may depend on how long the drug was taken and the amount of the dosage. Treatment with antipsychotic drugs plus high doses of vitamins found less chances of getting TD. Vitamins typically included vitamin C, niacin, vitamin B_6, and vitamin E in varying dosages.

TREATMENT OF TARDIVE DYSKINESIA

After noticing symptoms of tardive dyskinesia in psychotic patients patients, discontinuation of medication or reduction in dosage is the first approach.

The first benzodiazepine drug was chlordiazepoxide hydrochloride, It is essentially a tranquilizer which functions as an anti-convulsant and a muscle relaxant. Benzodiazepine drugs are highly effective at preventing convulsions such as are suffered by epileptics. They have also been used for patients with mental disorders and anxiety disorders. Because of these indications, it was thought that the drug might possibly make an effective treatment for tardive dyskinesia.

Amine-depleting medications actually reduce the levels of dopamine in the brain as well as serotonin. The most effective of these appears to be tetrabenazine. (Which are classified as dopamine antagonists and are designed to block signals from the brain to targeted cells), treating the condition is not as simple as removing the medication. Tetrabenazine has been effective in relieving the symptoms of tardive dyskinesia; it is not without its own side effects. These may include akathisia, a compulsive need to pace back and forth accompanied by inner feelings of anxiety and paranoia, dizziness, sleep difficulties or drowsiness and fatigue, and Parkinsonism (tremors and muscular weakness associated with Parkinson's disease).

Scientific evidence has indicated that marijuana (cannabis) has great potential to help patients manage symptoms of a number of diseases. Research in this area has had mixed results. While some studies have shown cannabis to be useful in helping patients manage the symptoms of tardive dyskinesia.

Since tardive dyskinesia is the result of drugs designed to block neurotransmitters (brain chemicals that transmit signals to the muscles and organ systems – primarily dopamine and serotonin), it would seem logical that one solution would be to enable these to function properly. Vitamin B6, or pyridoxine, is one that is necessary for the production of serotonin and the formation of myelin (an important part of the nervous system). Vitamin B6 is also an anti-oxidant, which may be helpful for the management of tardive dyskinesia symptoms. Preliminary research suggests that some tardive dyskinesia patients benefit from taking pyridoxine supplements. It should be noted that while Vitamin B6 is safe in low to moderate does (or when absorbed through food), but excessive doses may cause allergic reactions in some individuals as well as nausea, vomiting, abdominal pain and headaches.

Vitamin E is also an anti-oxidant, which is known to neutralize destructive "free radicals" (highly reactive

oxygen molecules). There is evidence indicating that such free radicals may in fact pay a part in the development of tardive dyskinesia symptoms.

Several management techniques involving the use of everything from herbs and vitamin supplements to electro-stimulation of the brain have been tried with varying degrees of success. One of these techniques employs a class of drugs known as adrenergic antagonists. In order to understand adrenergic antagonists (an antagonist inhibits a process, while an agonist stimulates it), it is helpful to review the nature and function of adrenergics in general. Adrenergics are drugs that mimic the action of adrenaline. An andregenic antagonist is a drug that essentially inhibits the production and function of adrenalin in much the same way that anti-psychotic (neuroleptic) drugs block dopamine receptors. In general, adrenergic antagonists are used to reduce tension and anxiety and promote relaxation. adrenergic antagonists may be helpful in treating tardive dyskinesia, Studies indicate that some patients do suffer from what is known as noradrenergic hyperactivity (an over-active adrenal gland), and they may benefit from certain types of adrenergic antagonists – primarily clonidine (an alpha-blocker used today primarily for sleep disorders and symptoms of ADHD) and proprandol (a blood pressure medication).

An agonist is a medication that enables a process or a biological response. An antagonist inhibits those same processes and responses. The symptoms of tardive dyskinesia are the result of the side effects of medications known as dopamine antagonists. Therefore, the use of dopamine agonists to treat these symptoms would seem logical, but this is not necessarily the case. Tardive dyskinesia is a complex movement disorder that affects every such patient differently. As a result, treatment is a highly individualized issue that varies from one person to another. A dopamine receptor agonist works in the reverse manner, activating the receptor process and enabling it to function properly.

Table 6: Treatment of Tardive Dyskinesia

S.No	Treatment class and examples	Comments
1	Cholinergic agents Dimethylethanolamine, lecithin and Meclofenoxate	The clinical effects of older cholinergic drugs are unclear, Cholinergic drugs should remain of interest to researchers but currently have little place in routine clinical work
2	Benzedlazepines	benzodiazepines may have an effect in neuroleptic induced tardive dyskinesia,
3	Calcium-channel blockers	The effects of calcium-channel blockers for antipsychotic Induced tardive dyskinesia are unknown, Theiruse is experimental and should only be given in the context of well designed randormsed studies,
4	Catecholamines *Noradrenergic drugs* Celiprolol, clonidine, disulfiram, fusaric acid, methyldopa, pindolol. Propanolol, oxprenolol and yohimbine, *Dopaminergic drugs* *Dopamine agonists* apomorphine, bromucnptine. Dopamine, hydergine and lisuride. *Dopamine antagonists:* oxiperomide, metoclopramide, papaverine and tiapride Dopamine depleters: oxypertine, reserpine, and tetrabenazine, Dopamine increasers: amantadine, amphetamine and Levodopa	The review provides little usable information for service users or providers and more well designed and reported studies are Indicated.
5	GABA ergic agents Baclofen, proqabrde and sodium valproate.	Evidence of the effects of baclofen, proqabrde or sodium valproate for people with antipsychotic-induced TD is inconclusive and unconvincing, Any possible benefits are likely to be outweighed bythe adverse effects associated with their use
6	Miscellaneous Ceruletide. Gamma-linolenic acid, oestrogen, lithium, phenylalanine and insulin	There is no strong evidence to support the everyday use of any of the agents Included in this review. All results must be considered inconclusive and these compounds probably should only be used within the context of a well-designed evaluative study,
7	Dose reduction or cessation of neuroleptics or specific neuroleptics	Limited data from small studies using neuroleptic reduction or specific neuroleptic drugs as treatments for TD did not provide any convincing evidence of the value of these approaches.

CONCLUSION

Tardive Dyskinesia is the extra pyramidal side effect of antipsychotic drugs can be effectively diagnosed by AIMS scale and managed by reducing dose of antipsychotic drugs. For the screening of Tardive Dyskinesia animal models are available and different drugs to treat Tardive Dyskinesia like cholinergic agents, benzodiazepines, calcium channel blockers, catecholamines etc.

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