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Review Article

A REVIEW ON TARDIVE DYSKINESIA

***A.Saravana Kumar and T.Sunil Kumar Reddy**

***RanD Ventura Biosciences Pvt. Ltd., Thyagaraja Nagar, Chennai-600 017, India.**

ABSTRACT

Orofacial dyskinesia or tardive dyskinesias are involuntary repetitive movements of the mouth and face. Dyskinesia refers to an impairment of voluntary movement. The resultant tics and other movements are often referred to as dyskinesias. Dyskinesia is sometimes caused by long-term use of anti-psychotic drugs or other dopamine antagonists like the antiemetic metoclopramide. This review mainly focused on the effect of anti-psychotic drugs or other dopamine antagonists can be tardive, meaning the dyskinesia continuous or appears even after the drugs are no longer taken.

Keywords: Orofacial dyskinesia or Tardive dyskinesias, Tardive dystonia, Tardive myoclonus.

INTRODUCTION

The presentation of TD is typical of a dyskinesia, with orofacial, axial, and extremity hyperkinetic movements. The movements worsen with stress and concomitant physical activity and diminish or disappear during sleep. TD onset is defining, in that all dyskinesias with their first onset within 6 months of ongoing antipsychotic treatment are diagnosed as TD. Consequently, it is expected that the diagnosis will be confounded by other categories of dyskinesia, including dyskinesias of schizophrenia and of the elderly [1,2]. TD is distinguished from Parkinsonism, the other major category of antipsychotic-induced movements, by being hyperkinetic, with delayed onset and delayed resolution after medication discontinuation, and by its contrasting pharmacology. The clinical course of TD varies by psychiatric diagnosis, age, sex, and concomitant medical or neurologic illness. Data from a prospective study of 971 young adult psychiatric patients followed for up to 20years indicated a increasing cumulative incidence rate of TD over the 20-year interval. The cumulative incidence of persistent TD was lower but increased proportionally [3]. Orofacial dyskinesias consist of tongue protrusion with licking of the lips, sucking and smashing movements.These data are consistent with a declining rate of TD over time, illustrated by the declining hazard rate (Table no.1)

[a]Hazard Rate is the rate of tardive dyskinesia occurrence per year among those remaining at risk. The number represents the average yearly hazard rate over the 5-year block of time.

Investigation of voluntary control of lip, jaw, and tongue movements in schizophrenic patients with and without tardive dyskinesia was conducted in twenty-two schizophrenic patients and 13 normal control subjectsof the patients, 11 had moderate to severe TD. Analyses were made of performance on pursuit tracking tasks to evaluate differences between TD and non-TD patients and between medicated and currently unmedicated patients. The results indicated significant group differences in voluntary orofacial motor control. The finding that many non-TD patients exhibited voluntary motor dyscontrol suggests that this may represent a disorder independent of the involuntary dyskinesia [4].

In a study the presence and severity of tardive dyskinesia were determined in 66 patients with chronic psychiatric disorders treated with chlorpromazine. The patients were classified according to the presence of antinuclear antibodies, the lupus anticoagulant, and the HLA antigen Bw44. The severity of orofacial dyskinesia was estimated using the Rockland Research Institute Scale.

Corresponding Author: **A. Saravana Kumar** Email: sarganjune1@gmail.com

Patients with autoantibodies and the Bw44 antigen had higher tardive dyskinesia scores than those with AAB without the Bw44 antigen and also patients without autoantibodies regardless of their HLA phenotype. These studies suggest that the presence of autoantibodies in association with the HLA Bw44 antigen is related to, and can be a predictor of, neurological complications of long-term chlorpromazine therapy [5].

TD and neuroleptic dosage were analyzed in relation to cognitive and motor tests of the Luria Nebraska (L-N) battery and to attentional evoked potentials (EPs) .Neuroleptic dosage was not directly correlated to any single motor or cognitive measure, or to TD indices [6].

Drugs that may cause tardive dyskinesia

Acetophenazine maleate	Fluphenazine
Amoxapine	Metoclopramide
Butaperazine maleate	Haloperidol
Carphenazine maleate	Molidone
Chlorpromazine	Loxapine
Chlorprothixene	Thioridazine
Risperidone	Perphenazine
Trifluoperazine	Mesoridazine

Aging is a major risk factor for development of TD, and other risk factors are sex, mood disorders, organic brain dysfunction, and early extrapyramidal side effects. There are conflicting reports on brain atrophy seen on neuroimaging and susceptibility to the development of TD.

TYPES OF TARDIVE DYSKINESIAS

- Tardive dyskinesia
- Classic orobuccolingual dyskinesia
- Tardive dyskinesia variants
- Tardive dystonia
- Tardive akathisia
- Tardive myoclonus
- Tardive tics
- Tardive tremor

VARIOUS TARDIVE DISORDERS

Classic orobuccolinguomasticatory syndrome

Classic orobuccolingual dyskinesia (OBLD) was the first type of TD described. It consists of stereotyped oral and facial movements, including twisting and protrusion of the tongue, lip smacking and puckering, and chewing. One of the early signs of OBLD is slow, writhing movements of the tongue in the floor of the mouth. Movements are confined to the orofacial area but sometimes spread to involve the extremities. The upper face is often uninvolved in TD, but blepharospasm may occur with tardive dystonia.Occasionally, diaphragmatic dyskinesia can result in dyspepsia and hypoxia. OBLD is frequently associated with tardive akathesia, tardive dystonia, and Parkinsonism. OBLD may cause dry mouth, dysarthria, and dysphagia. OBLD is usually associated with long-term DBA therapy but may occur in either situation.

Differential diagnosis of orobuccolingualdyskinesias

- Spontaneous dyskinesia of elderly(usually dystonic)
- Hereditary choreas
- Basal ganglia strokes
- Systemic lupus erythematosus
- Edentulous dyskinesia
- Other drugs causing dyskinesias

Levodopa	Amphetamines
Cocaine	Tricyclic antidepressants
Cimetidine	Flunarizine
Antihistamines	Phenytoin

Tardive akathisia

Akathisia is characterized by an inability to sit still accompanied by an inner sense of restlessness. Persistent akathisia may occur as a subtype of TD as opposed to acute akathisia, which is apparent within a short period of the beginning of DBA therapy. Persistent akathisia is defined as an occurrence present for at least 1 month when the patient is receiving a constant DBA dose. It occurs in 20% to 405 of DBA-treated patients with schizophrenia.

Tardive dystonia

Multiple reasons exist to differentiate classic TD from tardive dystonia. The abnormal movements are distinct from those of classic TD .Whereas classic dyskinetic movements are rapid and stereotyped dystonic movements are slower and twisting. Whereas TD seems to occur more commonly in elderly women, tardive dystonia seems to be more common in younger patients and to have no preditection for either sex. Moreover, anticholinergic drugs tend to worsen classic TD but beneficial in tardive dystonia. Tardive dystonia tends to be more persistent than classic TD.

Tardive tics or tardive tourettism

Rarely, motor and vocal tics appear for the first time in patients receiving long-term antipsychotic therapy. The tics may be accompanied by coprolalia.

Tardive myoclonus

Tardive myoclonus has been described as a late complication of prolonged neuroleptic therapy. Usually it is a myoclonus of the upper extremities, and associated movement disorders are common.

Tardive tremor

It is said to be more postural and kinetic than the rest tremor in drug-induced Parkinsonism and usually is not associated with other parkinsonian signs. This tremor

responds poorly to the dopaminergic drugs used in Parkinson's disease.

MOVEMENT DISORDERS

Movement disorders can be divided into conditions in which the problem is primarily reduced movements (hypokinesis) or excessive movement (hyperkinesis). The hypokinetic category is predominantly Parkinsonism and its various subgroups, whereas problems characterized by excessive (hyperkinetic) movement include dystonia, chorea, tics, myoclonus, and tardive syndromes.

Hypokinetic disorders

The major one among this is Parkinsonism. Degeneration of the substantianigra is responsible for the motor signs (rigidity, bradykinesia, resting tremor, and imbalance) of Parkinson's disease, damage to other portions of the exrapyramidal motor system may also give rise to Parkinsonism .Thus, parkinsonian motor signs may develop after lesions of caudate putamen, or globuspallidus.

Hyperkinetic disorders

Excessive movements may take on a variety of well-defined forms, including myoclonus, dystonia, tics or tremor. Some less well-defined hyperkinetic movements also deserve discussion, including spasms, stereotypies, and myorhythmias.This category also encompasses the tardive disorders, which have a variety of manifestations.

H**yperkinetic movements in response to an irresistible internal urge**

This category includes tic disorders and hyperkinetic movements provoked by akathisia (inner restlessness).Certain stereotypies (stereotyped motor behaviors) also belong with this group, sharing features with tics.

Tic disorders

Tics are simple or complex motor acts occurring in response to an urge to perform the movement. Usually they are manifested as a single type or a few repeated types that are stereotyped. These stereotyped movements may be simple or complex. Shrugging, blinking, grimacing, and grunting are examples of simple tics. More complex tics might include kicking, squatting, or vocalizing words.

Motor responses to akathisia

Akathisia implies an inner restlessness, which if severe, provokes movement as a means of relief. This may occur as a consequence of administration of dopamine antagonist drugs (e.g., neuroleptic or antiemetic agents) either early, as a reversible adverse event, or later as a tardive disorder (often irreversible).The motor responses to akathisia take on a variety of forms, but the usual appearance is an inability to sit still. Repetitive leg crossing and uncrossing, weight shifting, pacing the floor, and similar movements, often attenuate the symptoms, form the objective motor component of akathisia [1].

G**eneral categories of abnormal hyperkinetic movements initiated outside conscious awareness**

Myoclonus, tremor, dystonia, and chorea are basic categories of hyperkinetic movements that originate outside conscious awareness. There is no primary subjective sensation that provokes these movements, and in some instances such as milder cases of chorea, patients may be unaware.

Myoclonus

Myoclonus is defined as sudden lightening-like jerks of a body part. The jerk, by definition, involves at least one entire muscle and displaces a body part. This is in contrast to fasciculation or myokymia which occurs in only a segment of muscle and does not result in movement across joints.Myoclonus emanates from the CNS, in contrast to fasciculation, which originate in anterior horn cells or more distally.

Tremor

Rhythmicity is the hallmark of tremor. Implies a regular rhythm with a relatively consistent periodicity. When assessing tremor, it is often a good idea to observe the tremor for more than just a few seconds, attending to the rhythmicity and frequency.

Dystonia

Dystonia implies an abnormal posture of one or more portions of the body with an inappropriate sustained contraction of musles. A dystonic foot may be involuntary inverted or a dystonic neck (torticollis) may be manifested as involuntary rotation to one side.Dystonia may be apparent only in certain situations or with certain tasks. For example, foot dystonia during walking may normalize during running or walking backwards. Only very circumscribed tasks may bring out the dystonia, such as so-called writer's cramp (task specific writing dystonia).

Chorea

Rapid, flowing movements of a part or parts of the body that are random in space and time characterize chorea. Patients may perform simple voluntary movements with a choreiform flourish. For example, voluntary touching of the nose may be preceded by a wide circling movement of the hand before the finger lands precisely on the target.

Ballismus

Ballismus is actually on one end of the chorea spectrum. It appears as violent, large amplified chaotic movements of a body part especially the proximal limbs. Typically occurrence is on only one side of the body and is hence designated"hemiballismus".Most often, a lesion of

the sub thalamic nucleus is responsible, but lesions of other extrapyramidal structures may occasionally cause a similar syndrome.

Athetosis

Athetosis is a slow, writhing involuntary movement of a distal limb. On close analysis, the appearance is actually that of chorea combined with dystonia.When the choreiform component is prominent, the term" choreoathetosis" may be applied. 'Athetosis" and "choreoathetosis" are terms that conventionally have most often been used in cerebral palsy.

Stereotypies and tardive syndromes

In the context of movement disorders,"stereotypy" implies a recurring and often complex movement that has a relatively fixed character. The concept of stereotypy also best characterizes some of the adventitious movements of tardive dyskinesia.. "Tardive dyskinesias" are involuntary movements of the mouth and face. Classic orobuccolingualdyskinesias are the most frequently recognized signs of tardive dyskinesia, and sometimes the terms for these two disorders are used interchangeably." Tardive dyskinesia" encompasses a wide variety of abnormal movements that develop in some patients receiving long-term treatment with drugs blocking dopamine receptors (e.g., neuroleptic and antiemetic agents).

Categories of abnormal hyperkinetic movements not originating in conscious awareness

Myorhythmia: palatal tremor (palatal myoclonus)

The term "myorhythmia" is reserved for slow, pendular, periodic movements; that is, a very slow tremor. The frequency is 1 to 3 cycles/sec, which is less than the 4 to 8 cycles/second typical rest tremor of Parkinson's disease. Myorhythmias are typically present at rest and may be exacerbated or attenuated by sustained posture or muscle activation. Palatal myoclonus is the prototypical myorhythmia

Spasms

Spasm is a very general term applied to a sustained hypercontractile state of muscle that consequently reduces mobility of the involved region. The origin may be peripheral, such as in hemifacial spasm or lumbar spasms secondary to lumbosacral nerve root compression or even muscle strain. Spasms may also have a CNS origin, such as in stiff-man syndrome.

MEDICATION - INDUCED MOVEMENT DIS ORDERS

Medication-induced movement disorders occur due to treatment with anti-psychotic medications. Most medication-induced movement disorders are caused by medications that block the action of dopamine, a neurotransmitter that allows communication between two neurons to take place and that is necessary for co-ordination of movements of different parts of body. When the receptor where dopamine is supposed to bind is blocked, certain movement-related side effects occur. All the medications that block dopamine receptors are called neuroleptics (e.g, haloperidol, chlorpromazine, and reserpine).

PATHOGENESIS OF TD

The major hypothesis which exists to explain the cause of tardive dyskinesia are:-

Dopamine supersensitivity hypothesis

Neuroleptic drugs appear to act in part by blockade of central dopamine receptors. This blockade has been postulated to then result in a state of "chemical denervation" of dopamine receptors in the striatum. Some of these altered receptors are regarded as then developing "denervation hypersensitivity". Those neurons whose dopamine receptors have become hypersensitive may then respond abnormally to any dopamine to which they are exposed. Besides receptor blockade, neuroleptics increase synthesis and blockade of the reuptake of dopamine, thereby presenting sensitized receptors with additional amounts of dopamine. These effects would be expected to aggravate a state of receptor hypersensitivity. If the blockade is complete at any receptor site, the receptor is prevented from receiving its normal neurotransmitter influence .Dopamine turnover studies are consistent with the gradual development of denervation hypersensitivity[7]. Cerebrospinal fluid levels of homovanillic acid, the major metabolite of dopamine, tend to increase acutely following the administration of neuroleptics. Although the neuroleptics block both types of dopamine receptors (D_1, D_2) the degree of blockade is different for the two populations. The dopamine facilitated neurons are blocked by levels of haloperidol or chlorpromazine that do not block the action of dopamine-inhibited receptor sites. Only with larger doses of the neuroleptics the dopamine inhibited blocked. This observation, together with the observation that tardive dyskinesias can occur independently of drug-induced Parkinsonism, suggests that the two disorders both relate to dopamine but to different receptor populations .One could visualize tardive dyskinesias as an abnormal hyperactive response of dopamine-facilitated receptors to dopamine, while Parkinsonism relates to a lack of response of the dopamine-inhibited receptors to dopamine [8].

Neuronal degeneration hypothesis

According to this TD is the consequence of neuroleptic induced neuronal loss, particularly in the striatum .Two interacting mechanisms has been proposed for the pathogenesis of cell damage:-

- Production of free radicals (Oxidative stress)
- Excitotoxicity

Dementia has been associated with drug-induced dyskinesias and has been suggested to support the role of underlying brain damage.

OXYGEN FREE RADICALS AND TD

"Free radical hypothesis" purporting to explain the pathophysiology of TD and suggesting novel therapeutic approaches for TD. This hypothesis points out that neuroleptic treatment activates oxidative processes in the brain. These, in turn increase free radical generation and may cause oxidative membrane and subcellular damage. The basal ganglia are particularly vulnerable to this effect, leading to the development of dyskinetic movement. Treatment with antioxidants might then prevent or reverse both the pathophysiology and symptomatology. The brain is particularly susceptible to free radical damage because of its high oxygen use, its high concentration of transition metals such as iron, manganese and copper (which acts as a catalyst for free radical formation), its low concentrations of antioxidants (e.g.: vitamin C and E) and low levels of the enzymes of the antioxidant defence system and because of its high concentrations of polyunsaturated fatty acids which are targets for free radical attack. While free radicals can damage most cellular (e.g. DNA, protein, and membrane lipids) their effects on functional neurophysiology are most likely a consequence of their ability to initiate an oxidative chain reaction known as lipid peroxidation cascade. Consequences of lipid peroxidation can include alterations in membrane fluidity, disruption of receptor-second messenger coupling, dysregulation of iron transport, shifts in transmembrane electrical potential, and formation of peroxide pores which can permit leakage of calcium. All of these membrane effects can transiently or permanently effects biological signal transmission and calcium leakage can cause swelling and functional cell shutdown and ultimately cell death.

Vitamin E is the major exogenous lipid-soluble antioxidant, and as it resides within the lipid membrane it can effectively disrupt the lipid peroxidation cascade, cells also can repair early membrane changes possibly through mechanisms involving phospholipase,A_2 which may preferentially remove oxidized fatty acids from membrane phospholipids. There are several mechanisms by which chronic treatments with neuroleptics may increase free radical formation and cause tissue damage. Catecholamine metabolism via monoamine oxidase produces hydrogen peroxide, and catecholamine themselves can be oxidized to quinines and semiquinones, which can generate free radicals. Further, in animals chronic neuroleptic treatment increases the accumulation of iron and manganese in brain, particularly the basal ganglia structures associated with movement disorders. Patients' treated with neuroleptics have elevated CSF indices of lipid peroxidation and copper compared to untreated control patients.

Prevalence of TD:-

Movement disorders were seen in psychotic patients before the neuroleptic era. In the recent study, 3 of 22(14%) schizophrenic patients who had never received medication met the research diagnostic criteria for probable spontaneous dyskinesia. However, epidemiologic evidence suggests that the prevalence of TD in medicated schizophrenic patients is far higher than in the pre-neuroleptic era, suggesting that TD is associated with neuroleptic therapy. Among individuals treated with neuroleptics the prevalence of TD is in the order of 10-15% in young population, 12-25% in more chronic patients, and 25-45% in very chronic patients. A mean prevalence of 24.2% was found in a meta-analysis of 76 studies including 39184 patients with a history of neuroleptic exposure. Estimates of severity have generally identified severe impairment in about 4-5%, moderate impairment in about 45% and mild impairment in about 50% of TD patients. All classes of dopamine blocking agents (DBAs) have been implicated in the development of TD. These include phenothiazines, such as chlorpromazine and thioridazine, and butyrophenones, such as haloperidol. DBAs like metoclopramide and prochlorperazine given for gastrointestinal disorders are also associated with the development of TD [9].

ANTIOXIDANT

The term antioxidant is defined as "any substance that delays or inhibits oxidative damage to target molecule".To be effective against free-radical-mediated cell disturbances, the antioxidants or free-radical scavengers must have several important characteristics.

PREVENTIVE ANTIOXIDANTS

To counter the harmful effects of ROS, antioxidant defence mechanism operates to detoxify or scavenge these reactive oxygen species. The antioxidant system comprises different types of functional components classified as first line, second line, third line and fourth line defenses. The first line defense comprises preventive antioxidants that act by quenching of superoxide anions, Catalase, glutathione peroxidase, glutathione reductase and non-enzymatic molecules like minerals and some proteins. Superoxide dismutase mainly acts by quenching of superoxide ($O^{\cdot}_2$), an active oxygen radical, produced in different aerobic metabolism. Catalase is a tetrameric enzyme, present in most of the cells that acts by catalyzing the decomposition of H_2O_2 to water and oxygen. Glutathione peroxide (GSH-Px) is a selenium containing enzyme which catalyses the reduction of H_2O_2 and lipid hydroperoxide, generated during lipid peroxidation, to water using reduced glutathione as substrate.

The antioxidant minerals include Selenium, Manganese, Copper, and Zinc and function primarily in the metalloenzymes . Selenium is required in some of the

immune mechanisms and biosynthesis of ubiquinone and ATP in mitochondria. The renal cortex, pancreas, pituitary and liver contain high amount of selenium. A deficiency of selenium produces hepatic necrosis, muscular dystrophy, necrosis cardiac muscle and other disorders in various experimental animals. Selenium and vitamin E both appear to be necessary for efficient scavenging of peroxides from cytosol and cell membrane, respectively. Manganese excerts its antioxidant action through mitochondrial SOD (MnSOD) which catalyses the dismutation of oxygen radical produced during aerobic metabolism in mitochondria. Copper is present in a number of metalloenzymes including cytosolic SOD, cytochrome oxidase, dopamine β-hydroxylase and ascorbic acid oxidase etc.Thisexcerts its antioxidant action through the cytosolic superoxide dismutase. Zinc is an element essential for normal growth, reproduction and other different functions of the body. It is a component of several enzymes like cytosolic superoxide dismutase, alkaline dehydrogenase, alkaline phosphatase, carbonic anhydrase etc Second line defence include glutathione (GSH) ,vitaminC,vitaminE (α-tocopherol),uric acid, albumin, bilirubin, carotenoids, flavanoids and ubiquinol. Glutathione (GSH 2-gamma-glutamyl-cysteinyl-glycine) is the most abundant non-protein thiol, synthesized in the liver and acts as a substrate for glutathione peroxidase enzyme. This also serves as a scavenger of different free radicals. β-carotene (pro-vitamin), vitamin C, vitamin E are some important antioxidant vitamins that cannot be synthesized by most mammals including human beings and therefore, are required from diet [10].

Glutamate-induced Excitotoxicity

L-Glutamate is the principal and ubiquitous excitatory transmitter in the central nervous system (CNS). Glutamate is widely and fairly uniformly distributed in the CNS and its concentration there is much higher than it is in other tissues. It has an important metabolic and neurotransmitter pools being linked by transaminase enzymes that catalyzes the interconversion of glutamate and α-oxoglutarate. Glutamate in the CNS comes mainly from either glucose, via the tricarboxylic acid (Krebs) cycle, or glutamine, which is synthesized by glial cells and taken up by the neurons, very little from the periphery. Glutamate is stored in synaptic vescles and released by calcium-dependent exocytosis, specific transporter proteins account for its uptake by neurons and other cells, and for its accumulation by synaptic vesicles [11].

Many studies have revealed that postsynaptic glutamate directly mediates striatal dopamine release via the stimulation of presynaptic N-methyl-D-aspartate (NMDA) receptors localized on nigrostriatal nerve terminals. In addition, NMDA receptors may indirectly affect dopamine release by modulating the release of other neuro-active molecules such as acetylcholine, and nitric oxide. On the other hand, dopamine has been demonstrated to have an inhibitory effect on glutamate release via dopamine D2 receptors located on corticostriatal dendrites and terminals. Preserving the balance of dopamine and glutamate release seems to be a major factor in maintaining normal striatal motor functions. Imbalance of dopaminergic-glutamergic functions could alter normal striatal activity, possibly resulting in motor abnormalities as in Parkinsonism. Moreover, neuroleptic treatment, which is known to block striatal dopamine receptors, has been shown to alter striatal glutamergic activity at both structural and functional levels. Thus, it is intriguing to speculate that neuroleptic-induced alterations in glutamatergic neurotransmission may play a role in TD pathophysiology [12].NMDA receptor activation has been reported to be accompanied by an enhanced production of reactive oxygen species (ROS), and oxidative stress is a component of glutamate-induced excitotoxicity.

Pharmacologic evidence has indicated the participation of a glutamergic component in the development of TD induced by acute reserpine treatment, because dizocilpine (MK-801), a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, blocked the haloperidol and reserpine induced orofacial dyskinesia. Glutamate uptake from the extracellular space is mediated by transport proteins located on the cell membrane of neurons and glia. Of particular significance, the glutamate transporter located on the plasma membrane contains reactive thiol groups in its structure and oxidation of these critical cysteinyl residues results in reduced glutamate uptake. Consequently, oxidant agents may produce neurotoxicity by increasing extracellular glutamate [13].

Diagram shows glutamatergic nerve endings forming synapses with a postsynaptic neuron containing N-methyl-D-aspartic acid (NMDA) receptor/channel complex. Neuroleptics can cause disinhibition of glutamatergic input through the presynaptic D2 receptor. The NMDA receptor has been shown to be regulated by glycine (Gly), which acts on an allosteric site of the receptor.Increased glutamate (Glu), N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG), and aspartate (Asp) concentrations in tardive dyskinesia may enhance postsynaptic NMDA conductance. In addition, superoxide dismutase (SOD) activity is reduced and protein carbonyl content is increased in TD.

Several markers for excitatory neurotransmission (i.e., *N*-acetylaspartylglutamate, *N*-acetylaspartate, aspartate and glutamate) and for oxidative damage (i.e., superoxide dismutase, protein carbonyl content, and lipid hydroperoxides) were measured in the CSF of schizophrenia patients under chronic neuroleptic treatment; about half of them exhibited the symptoms of tardive dyskinesia. ergic neurotransmission and increased free

radical generation and oxidative stress -can produce a vicious cycle of neuronal insults in tardive dyskinesia as indicated by the arrowed lines [14].

Animal models of TD

Various animal models employed for the screening of TD are:-

Reserpine induced Orofacial dyskinesia

Reserpine (1.0 mg/ kg, s.c) was repeatedly administered to rats on alternate days for a period of 5 days (days 1, 3 and 5) to induce oral dyskinesia.

Neuroleptic-induced orofacial dyskinesia

Haloperidol (1.0 mg/kg, i.p), chlorpromazine (5.0 mg/kg, i.p), or clozapine (2.0 mg/kg, i.p) is given chronically to rats for a period of 21 days to induce oral dyskinesia [15].

Isoniazid-induced orofacial dyskinesia

Isoniazid (1, 2, 5 and 10μmol/rat) is administered intracerebroventricularly to male wistar rats for the induction of vacuous chewing movements (VCMs)[16].

Apomorphine-induced orofacial dyskinesia

Orofacial dyskinesia is induced by a single i.m injection of 0.1mg/kg apomorphineHCl 1% in monkeys [17].

Amphetamine microinjection

Microinjection of amphetamine (20μg/0.5μl) into a circumscribed sub region of the striatum specifically produces intense oral stereotypy. The behavior elicited by amphetamine-induced stimulation of this area may represent a simple animal model in which to study certain orofacialdyskinesias [18].

Administration of endomorphin-1

Bilateral administration of endorphin-1 in the globuspallidus of rats induced orofacial dyskinesia. This effect was dose-dependent and at the highest dose tested (18pmol per side) was sustained during the 60 min of observation, indicating that endomorphin-1 does not induce rapid desensitization of this motor response [19].

Microinjection of sigma ligands

Microinjection of the high affinity sigma ligands, di-o-tolylguanidine or haloperidol (0-10nmol/0.5μl), produced a marked increase in vacuous chewing and facial tremors in rats[20].

The effect of spirulina maxima on haloperidol induced tardive dyskinesia and oxidative stress was studied in rats. Spirulina maxima suspended in 1% tween 80 at a dose of 45, 90 and 180mg/kg were administered by gavage along with haloperidol from 21st day to 49th day of treatment. Spirulina supplementation at a dose of 180mg/kg significantly improved enzymatic and non-enzymatic antioxidants and decreased the tardive dyskinesia induced by haloperidol [21].

It is reported that rolipram, a cAMPphosphodiesterase inhibitor suppresses oro-facial movements in rats chronically treated with haloperidol. Rolipram (0.1-1.0 mg/kg, i.p) suppressed spontaneous chewing movements and tongue protrusions in a dose dependent manner [22].

Studies were conducted on the possible involvement of prostaglandins in haloperidol-induced orofacial dyskinesia in rats. Indomethacin, a nonselective cyclooxigenase inhibitor dose-dependently (5-20 mg/kg) suppressed the vacuous chewing movements count in haloperidol-treated animals[23].

Interactions of the subthalamic nucleus, subpallidal area in orofacial dyskinesia and role of GABA and glutamate in male rats were studied. The study shows that inhibition of GABA in the lateral hypothalamic area induces orofacialdyskinesia (OFD) in the cat. This OFD effect needs the sub-pallidal area for its expression and is mediated via glutamergic neurotransmission [24].

Effects of valproic acid was studied (the GABA mimetic drug) on an animal model of tardive dyskinesia. Male wistar rats received two injections of control solution or 1mg/kg reserpine separated by 48 hr. Twenty-four hour later , animals were treated with 50, 100 ,or 200mg/kg valproic acid or control solution and were observed for quantification of orofacial movements and open-field general activity [25].

Concomitant development of oral dyskinesia and memory deficits in reserpine treated male and female mice was studied. Male and female mice received 1.0mg/kg reserpine or saline subcutaneously on day 1, on days 3, 6 and 8, the frequency of vacuous chewing movements (VCMs) was quantified. On day 6, the plus-maze discriminative avoidance task was performed [26].

Relationship of orofacial movements to behavior repertoire was assessed topographically over the course of 6 month haloperidol treatment followed by 4 month withdrawal. Animals were injected with haloperidol decanoate 28mg/kg i.m, or vehicle, every 3 weeks for 27 weeks, and then maintained without treatment for a further 18 weeks. Immedietly before each injection and during withdrawal, VCMs and other topographies of behaviour were assessed[27].

The preventive role of antioxidants (Selegiline and Vitamin E) in a rat model of tardive dyskinesia was reported. Rats were treated with fortnightly injections of fluphenazinedecanoate for 12 weeks, and examined at

baseline and at fortnightly intervals for vacuous chewing movements, mouth tremors and tongue protrusions[28].The important mechanisms underlying the protective potential of alpha-tocopherol (Vitamin E) against haloperidol associateted neurotoxicity in rats were reported [29].

Table 1

Neuroleptic Exposure (y)	Tardive Dyskinesia Cumulative Incidence, (95% CI)	Persistent Tardive Dyskinesia, (85% CI) Cumulative Incidence	Tardive Dyskinesia Hazard Rate[a]
1	.05 (.04–.07)	.03 (.02–.04)	—
5	.27 (.23–.31)	.20 (.17–.23)	6.1%
10	.43 (.38–.47)	.34 (.30–.39)	4.7%
15	.52 (.46–.57)	.42 (.36–.47)	3.3%
20	.56 (.50–.63)	.49 (.41–.57)	2.1%

Table 2. Drug used to treat tardive dyskinesia and variants

Drug Starting dose	Maximum dose	Drug Starting dose
Clonazepam	0.25 mg q.i.d	2mg q.i.d
Baclofen	10mg q.d	20mg q.i.d
Tetrabenazine	25mg q.d	50mg t.i.d
Vitamin E	400 IU b.i.d	1000 IU b.i.d
Trihexyphenidyl	2mg q.d	20mg q.i.d
Botulinum toxin	variable	variable

Fig 1. Hypothetical Model of Glutamatergic Synapse in Tardive Dyskinesia

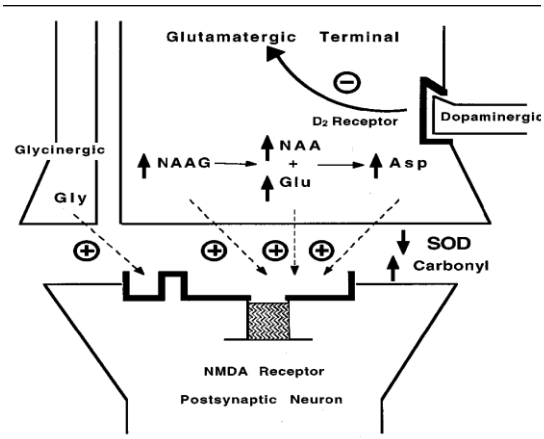
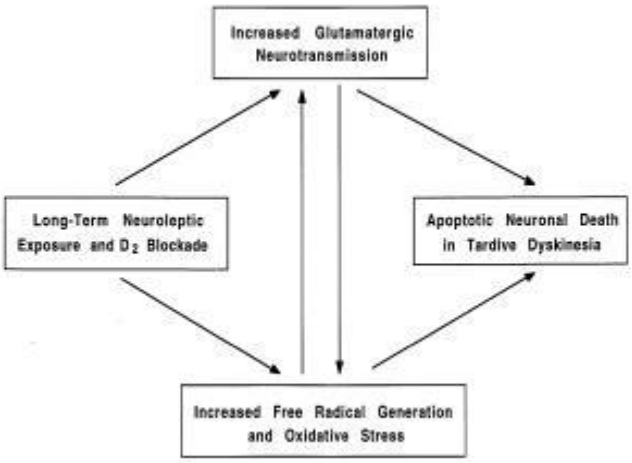


Fig 2. Hypothetical Model of Neuroleptic-Induced Oxidative Stress and Neurotransmission in Tardive Dyskinesia



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