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A REVIEW ON TARDIVE DYSKINESIA AND ITS MANAGEMENT

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ABSTRACT

Tardive dyskinesia is a movement disorder and it is usually associated with the chronic use of first generation antipsychotics which includes involuntary rapid movements of face and body like grimacing, tongue movements, lip smacking, lip puckering, pursing of the lips, excessive eye blinking, rapid and involuntary movements of the limbs, torso, and phalanges. With the availability of second generation antipsychotics, the risk of tardive dyskinesia is decreased to some extent. The pathophysiology of tardive dyskinesia was not completely understood but the possible mechanisms include post-synaptic dopamine receptor hypersensitivity, striatal GABA neurons abnormality, and striatal cholinergic inter-neurons degeneration. There is no evidence based treatment which is effective in treating the tardive dyskinesia till date. Several drugs have been tried to determine their efficacy in decreasing the symptoms of tardive dyskinesia.

KEY WORDS: Tardive dyskinesia, Dopamine, Clozapine, Vitamin E, Abnormal Involuntary Movement Scale.

INTRODUCTION

Tardive (delayed) dyskinesia(TD) is a neurological syndrome characterized by repetitive, involuntary, purposeless movements caused by the long-term use of certain drugs called

neuroleptics which are used for psychiatric and neurological disorders. [1] The original description on tardive dyskinesia was published by Schonecker in 1957, about five years after the commencement of neuroleptic treatment in psychiatry. [2] The most common symptoms of tardive dyskinesia are grimacing, tongue movements, lip smacking, lip puckering, pursing of the lips, excessive eye blinking, rapid and involuntary movements of the limbs, torso, and phalanges. [3]

The use of neuroleptic agents often leads to delayed onset of the symptoms of the tardive dyskinesia. Amongst several studies being performed, the incidence of tardive dyskinesia is more common in older patients than in adults even with the low doses of neuroleptics as a short term treatment[4] and the overall incidence is about 20%–40% in the patients who have undergone the treatment with the neuroleptics for different medical conditions. [5,6,7] Pathophysiology of TD remains poorly understood. Various neurochemical hypotheses have been proposed for the development of tardive dyskinesia and it is believed to be the result of chronic blockade of dopamine receptors. The hypotheses include dopaminergic hypersensitivity, disturbed balance between dopamine and cholinergic systems, dysfunctions of striato-nigral GABA ergic neurons and excitotoxicity. [8] The best preventive measures of TD is to start with the smallest effective dose of the safest drug and the Close monitoring for features of TD during the treatment with neuroleptics. [9] Several drugs are used in the management of the Tardive Dyskinesia and the first step in the management is to prescribe the neuroleptics evidenced to have the lower rates in causing TD and the most frequently prescribed drugs are tetrabenazine, benzodiazepines and vitamin- E, while the less commonly prescribed drugs are amantidine, amino acids, calcium antagonists, melatonin, donepezil etc.

SIGNS AND SYMPTOMS OF TARDIVE DYSKINESIA

The symptoms of tardive dyskinesia often resemble Tourette's syndrome or Parkinson's disease. Symptoms of tardive dyskinesia should develop atleast after two months of exposure to a dopamine blocking agent (or 1 month if the patient is 60 years or older); while the patient is on medication or within 4 weeks of withdrawal from an oral agent (8 weeks from long-acting injectable medication). The patient must show involuntary movements of the tongue (e.g., twisting, protrusion), jaw (e.g., chewing), lips (e.g., smacking, puckering), trunk, or extremities. Patterns of movements may include rapid, jerky and non-repetitive in nature (i.e., choreiform); slow, continuous and sinuous movements (i.e., athetoid); or rhythmic

movements). [11] Abnormal Involuntary Movement Scale (AIMS) is used to rate symptom severity and the Movements are scored on a scale of 0 (none) to 4 (severe). [12]

Etiology

TD most commonly occurs due to the chronic exposure to Dopamine receptor blocking agents, such as antipsychotics (typical and atypical neuroleptics). The typical antipsychotics are most likely to cause tardive dyskinesia than the atypical antipsychotics. The "Typical" antipsychotics tightly bind and remain clinged to Dopamine receptors for a longer time (a few days) than "atypical" agents and therefore, they have a stronger antipsychotic effect but much higher propensity to cause TD than the "atypical" antipsychotic drugs, which have a relatively low degree of Dopamine receptor antagonism and they tend to have a rapid (12–24 hours after a single dose) dissociation from the Dopamine receptors, thus presumably explaining the lower risk of TD.[13] Post-clozapine Second generation antipsychotics (SGA) still affect the dopamine D2 receptor less likely than First generation antipsychotics (FGA). Hence the chance of Extrapyramidal symptoms (EPS) do occur but tend to be less severe. Tarsy et al. reported that except clozapine and quetiapine other atypical antipsychotics have some evidence of causing TD. Weiden pj et al. stated that incidence of EPS differ amongst the SGAs, with high doses of risperidone associated with the most and clozapine and quetiapine with the fewest EPS. [14]

A number of non-neuroleptic compounds Anticholinergics like Benzhexol, Biperiden, Ethopropazine, Orphenadrine, Procyclidine, among the Mono amino oxidase inhibitors (MAOIs) phenelzine and in Selective Serotonin Reuptake Inhibitors (SSRIs) like fluoxetine, sertraline, Trazodone, Tricyclic antidepressants (TCAs) like amitriptyline, amoxapine, doxepin, imipramine, Antiemetics like Metoclopramide, Prochlorperazine, Antiepileptic drugs like Carbamazepine, Ethosuximide, Phenobarbital, Phenytoin, Antihistamines, Antimalarial drugs like Chloroquine, Antiparkinson agents like Bromocriptine, Carbidopa-levodopa, Levodopa, Anxiolytics like Alprazolam, Biogenic amines like Dopamine, Mood stabilizers like Lithium, Oral contraceptives like Estrogens, Stimulants like Amphetamine[15] are associated with dyskinesia that may be resolved with dose reduction or discontinuation of these drugs.

PATHOPHYSIOLOGY

A sustained D_2 receptor blockade resulting in receptor hypersensitivity is the most common hypothesis explaining the development of tardive dyskinesia.[11] The neurotransmitters

implicated in the pathophysiology of tardive dyskinesia includes the post-synaptic dopamine receptor hypersensitivity, striatal Gamma Amino Butyric Acid (GABA) neurons abnormality, and striatal cholinergic inter-neurons degeneration. [9] Clozapine's decreased propensity to induce tardive dyskinesia and its multiple neuro-receptor effects (e.g., binding to 5-HT_{1C}, 5-HT_2, and 5-HT_3 receptors) suggest a role for serotonin as well. Serotonin-containing neurons interact with the dopaminergic neurons in the substantia nigra and ventral tegmental areas. Genetic studies indicate a possible relationship with polymorphisms in the dopamine-2 receptor (DRD2), dopamine-3 receptor (DRD3), dopamine transporter (DAT1), and the serotonin 2A receptor genes. Oxidative stress and cell death secondary to increased glutamanergic neurotransmission is caused by the blockade of pre-synaptic dopamine receptors has also been postulated. [11]

Rosengarten et al proposed that TD may be the result of an imbalance in dopaminergic receptor function. [9] Another theory states that the TD may arise partly from the brain damage caused by the free radicals generated by the schizophrenic treatment. [16]

Incidence

The onset of TD is typically insidious; beginning several years after the initiation of treatment.[9] The incidence of tardive dyskinesia is higher in patients exposed to typical antipsychotics than exposed to atypical antipsychotics and the systemic review lasted for 1 year provided that risk is not absent with atypical antipsychotics but is significantly low i.e., between one fifth and one tenth of the typical antipsychotics, and the incidence is lower in patients exposed to single antipsychotic drug than the multiple antipsychotic drugs. Age is the most consistently replicated risk factor for incidence studies[17] and the incidence of TD is higher among the older patients than younger patients with both the typical and atypical antipsychotics. On comparision of the typical and atypical antipsychotics in older patients for developing tardive dyskinesia, the risk is higher with the typical antipsychotics and one recent study suggest that, the older patients treated with the typical antipsychotics were about as twice as likely to develop tardive dyskinesia than patients treated with atypical antipsychotics. Treating older patients with lower dosed antipsychotics, than the younger patients may reduce the risk of tardive dyskinesia. [18] In older patients (55 years or older), the onset of tardive dyskinesia is 25 % at 1 year, 34 % at 2 years, and 53 % after 3 years. The rate of onset is three to five fold higher in older patients than in younger patients. [11]Among all the atypical antipsychotics in both older and younger patients many studies shown that

clozapine does not develop tardive dyskinesia for many years. Next to clozapine, olanzapine, resperidone and quiteapine had lower rates of tardive dyskinesia than compared to haloperidol. [18]

Risk Factors

Risk factors include increasing age, female sex, pre-existing parkinsonism, previous brain damage, antipsychotic treatment duration, and exposure to FGAs, [11] alcohol and substance abuse, concomitant use of lithium and anti-parkinsonian agents, diabetes, HIV positivity, early extrapyramidal symptoms. [9]

Treatment

Some of the proposed guidelines for the treatment of tardive dyskinesia are:

1. Reducing the dose of the causative antipsychotic or switching over to clozapine, after tapering off the offending antipsychotic drug slowly.
2. Dopamine-depleting drugs -Reserpine (1 to 8 mg/day), Tetrabenazine (25 to 150 mg/day).
3. GABA-enhancing drugs Clonazepam (1 to 4mg/day), Valproate, Vigabatrin, Baclofen,

4) Antioxidants: Vitamin E 800 IU/bid. [19]

Second Generation Antipsychotics

With the increasing use of SGAs, fewer episodes and less severe symptoms of tardive dyskinesia are seen. For this reason, patients on FGAs are generally switched to a newer agent if possible. [11] Prospective studies lasting 6 months or more are consistent in demonstrating a significantly lower risk of TD with new generation drugs (i.e., clozapine, risperidone, olanzapine, quetiapine) than haloperidol, the most common comparator FGA. Fewer data are currently available with ziprasidone and aripiprazole, but early experience certainly suggests a low risk with these newer drugs as well. [20] Christoph U. Correll, M.D.et al. suggested that 11 long-term studies support that use of second-generation antipsychotics have a reduced risk for tardive dyskinesia when compared to first-generation antipsychotics, although the doses of haloperidol used in the comparator studies were relatively high. [21]

Clozapin: Clozapine is an early atypical antipsychotic drug and was first developed in 1961 but it is arrived in the market 1971 and it is withdrawn from the market after 4 years because of the development of agranulocytosis. In 1980, Food and Drug Administration (FDA) have approved clozapine for this use under the condition of regular blood screening. [22] Clozapine have superior efficacy and to cause fewer motor adverse effects than typical drugs[23] and the

rates of tardive dyskinesia is low among patients treated with clozapine.[18] Clozapine has also shown to reduce the dyskinetic movements in patients with tardive dyskinesia. [24]It is also useful in patients with neuroleptic resistant schizophrenia and in patients with treatment resistant illness.

Spivak B conducted a study to investigate the short term (18 weeks) use of clozapine in the treatment of extrapyramidal symptoms in patients with neuroleptic resistant schizophrenia and the assessment of extrapyramidal symptoms was done once weekly for 18 weeks using AIMS scale and Simpson Angus Rating Scale and at the end of 18 weeks, patients on the treatment of clozapine improvement of tardive dyskinesia is 74%, parkinsonism is 69%, chronic akathesia is 78% and concluded that the relatively low doses of clozapine are effective for the treatment of neuroleptic-induced extrapyramidal syndromes in neuroleptic-resistant chronic schizophrenic patients. [25]

Essali A et al. showed that patients with clozapine had lower relapses than patients treated with typical antipsychotics and clozapine is more acceptable in long term treatment than typical antipsychotics. [23]

Dr. John Kane, has spent several years studying tardive dyskinesia and the effects of various drugs and he concluded that clozapine administered concurrently with a second neuroleptic medication known as sulpride, posed the lowest risk of patients developing tardive dyskinesia symptoms. [22]

Vitamin E: Vitamin-E is an anti-oxidant, a substance that works to neutralize free radicals in the body. The free-radicals may play a vital role in the development of tardive dyskinesia. Hence vitamin E might help to prevent or treat the tardive dyskinesia. Several studies were done to determine the efficacy of vitamin E in treating or reducing the symptoms of tardive dyskinesia, amongst them, most of the studies suggested that vitamin E is beneficial in reducing the symptoms or treating the tardive dyskinesia and some studies suggested that there is no role of vitamin-E in treating tardive dyskinesia. [16] Soares kv et al. conducted a review to determine the efficacy of vitamin-E in treating tardive dyskinesia and several controlled trails are included in this study and they concluded that people who had not taken vitamin-E have shown the deterioration of symptoms of tardive dyskinesia , but it showcased no difference in the presence of adverse effects. [26] Sajjad sh conducted a preliminary study over 7 months with the different doses of vitamin-E in order to determine the efficacy of

vitamin E in treating tardive dyskinesia, 20 patients were included in this study from which, 11 patients (treatment group) and 9 patients (control group)] and the dose of vitamin-E is increased from 600mg to 1100mg over 7 months and the severity is rated on the AIMS score. Based on this scale, there is significant and sustained reduction in the severity of tardive dyskinesia and it suggests that vitamin-E is worth enough to treat tardive dyskinesia and optimum dose for treating is 1600 mg per day. In addition, there may be a dose related therapeutic effect of Vitamin-E in TD. [27]

Tetrabenazine: Tetrabenazine is a benzoquinolizine derivative which depletes pre-synaptic dopamine and serotonin storage and antagonizes post-synaptic dopamine receptors. [28] Tetrabenazine is approved by FDA [29] to treat one specific symptom of hungtinson's disease which is called "chorea" a condition that is characterised by irregular involuntary muscular contractions that usually radiate from one muscle to other. [30] Although the drug is described to have the dopamine depleting activity, it actually does it to facilitate the metabolism of dopamine. Tetrabenazine may benefit in managing the symptoms of tardive dyskinesia which is unresponsive to other treatment options as the abnormal movements of tarive dyskinesia may result from the over activity of dopaminergic neurons in the basal ganglia.[31]Several studies demonstrate the beneficial effects of tetrabenazine in managing the symptoms of tardive dyskinesia but its use is limited because of its high cost and clinically significant adverse effects such as depression, parkinsonism, and somnolence. [29]

Hajime Kazamatsuri, MD et al. demonstrates that the tetrabenazine reduces the frequency of abnormal movements of tardive dyskinesia at the dosage of 150 mg/day. [31] Joseph Jankovic, MD and Jennifer Beach, RN conducted a study by including 526 patients with severe hyperkinetic movement disorders treated with tetrabenazine and adequate follow up is done and the response is rated on the scale of 1 to 5 (1-marked improvement,4-no response and 5-worsening) was assessed initially and at the last visit. A score of 1 is recorded in 89.2% of patients and this study concluded that tetrabenazine is safe and effective for the treatment of hyperkinetic movement disorders such as refractory tardive dyskinesia. [32] William G. Ondo et al. conducted a study by including 19 patients in the mean of 20.3 weeks at the mean dose of 57.9mg/day assessed by using AIMS score and concluded that tetrabenzine is well tolerated and there is significant improvement in the AIMS scores. [33]

Reserpine: Reserpine is an inhibitor of vesicular monoamine transport there by depleting the stores of presynaptic dopamine. Reserpine is used to treat hypertension and is also used to

reduce the symptoms of tardive dyskinesia. It appears to be most effective, when the patient is no longer on a neuroleptic treatment. [34] Data was insufficient to support the efficacy of reserpine in treating the tardive dyskinesia. [35] Only one randomized double blind placebo controlled trail demonstrates the efficacy of reserpine in treating tardive dyskinesia [36] and a case study was reported stating that reserpine improved the symptoms of tardive dyskinesia during the treatment; but appeared to aggravate the underlying illness, as evidenced by increased symptoms after discontinuation of the reserpine. [37] Its use is limited by the presence of severe adverse effects (worsening of parkinsonism, depression and sedation). [38]

Clonazepam: Clonazepam is a benzodiazepine with the anti-epileptic and anti-anxiety effects and is also used as an effective treatment for tardive dyskinesia. Benzodiazepines have several advantages over other anti-dyskinetic drugs in treating tardive dyskinesia. The authors conducted a controlled study of clonazepam versus the active placebo of phenobarbital in 21 psychiatric patients with tardive dyskinesia. Both the drugs significantly reduced the dyskinetic movements: clonazepam had a stronger effect on oro-facial dyskinesia. Clonazepam is more effective in the patients who receive low doses of neuroleptics than in patients taking high doses of neuroleptics. [39] In another study, the authors tested the benzodiazepine (clonazepam) in a 12-week, double-blind, placebo-controlled, randomized crossover trial in 19 chronically ill patients with tardive dyskinesia who are on the neuroleptics. They found a 35% decrease in dyskinesia ratings with clonazepam treatment. [40] Paranthaman Sethupathi Bhoopathi1 et al. Conducted a review to determine the effects of benzodiazepine in tardive dyskinesia by including the various studies which used benzodiazepine as an adjunctive treatment, amongst them, a few studies showed that, benzodiazepine use do not show any change in tardive dyskinesia and some studies concluded that abnormal movements score is reduced by using benzodiazepine as an adjunctive treatment. [41]

GABA Amino Butyric Acid Agonists: The reduced GABA activity in the nigro-striatal pathway which controls the motor functions is one of hypothesis in the development of tardive dyskinesia along with the dopaminergic hypersensitivity. [42] So, GABA agonists may have the potential to reduce the symptoms of tardive dyskinesia and hence the trails have been performed to determine the efficacy of GABA agonists (valproate, vigabatrin, baclofen) in treating TD. [43]

Sodium valproate: Sodium valproate being an antiepileptic drug posse the GABA agonistic properties and it increases the levels of GABA in the brain and reduce the symptoms of tardive dyskinesia. Some studies have demonstrated that sodium valproate is effective in reducing the symptoms of the tardive dyskinesia. Casey DE, et al. suggested that sodium valproate increases the GABA levels in the brain and though not completely resolved, moderately reduced the symptoms of tardive dyskinesia with a dose of 900-3000mg/day and it is measured with the help of tremorgraph and rating scales. [44] R. Chadda and P. Kulhara conducted a study which included 15 tardive dyskinesia patients treated with sodium valproate in the dosage of 1200mg/day for 4 weeks assessed by using dyskinesia scales, after the 4 weeks there is statistically significant improvement is observed. [45]

Baclofen: Baclofen is a GABA-like drug which passes through the blood-brain barrier and reduces the neuroleptic-induced hike of dopamine turnover in TD. The baclofen is supposed to exert its action by inhibiting the dopaminergic activity but do not increase the dopaminergic hypersensitivity. Some studies demonstrated that baclofen is effective than placebo in neuroleptic induced tardive dyskinesia patients. S. Korsgaard et al. conducted a double blind cross over trail which included 20 female neuroleptic induced tardive dyskinesia patients and compared the efficacy of baclafen and placebo. 15 patients have shown the improvement on baclofen. [46] Reduction of hyperkinesias by baclofen was reported in double blind cross over study. [47]

Vigabatrin: Vigabatrin is a GABA agonist which increases the levels of GABA by replacing GABA as a substrate for the action of catabolic enzyme GABA transaminase and thus, the neuronal GABA levels are elevated.[48]There are only a few reports available confirming the efficacy of vigabatrin in tardive dyskinesia.

Less Commonly Prescribed Drugs

Amantidine: Amantidine is an N-methyl-D-Aspartate antagonist which is beneficial in reducing the symptoms of tardive dyskinesia because of its glutaminergic effects. [49] Pappa s et al.conducted a double blinded placebo controlled cross over design in order to demonstrate the efficacy of amantidine in treating tardive dyskinesia without effecting the mental status of the patient by including 22 patients and compare the amantidine (100mg) and placebo for 2 weeks and efficacy is assessed by using AIMS scale. By using amantidine the severity of tardive dyskinesia movements are improved significantly without effecting the cognitive state. Amantidine is safe and effective for the treatment of tardive dyskinesia[50] Amantidine

reduced TD movements with neuroleptics in the first 7 weeks, it should be considered as an short term treatment of TD. [51]

Amino Acids: The occurence of tardive dyskinesia in schizophrenic or neuroleptic taking patients is due to lesser ability to clear the large neutral amino acid (LNAA) and phenylalanine. Branched chain amino acids BCAA) are beneficial in improving the symptoms of tardive dyskinesia by increasing plasma LNAA/BCAA ratio and decreases the levels of phenylalanine. [52] Mary Ann Richardson, Ph.D. et al. conducted a study to determine the efficacy of BCAA in tardive dyskinesia by including patients with long history of antipsychotics and long standing tardive dyskinesia and administered high doses of BCAA for 3 weeks resulting in the improvement of tardive dyskinesia symptoms. [53]

Botulinum Toxin: Some studies suggested that botulinum toxin is beneficial in improving the symptoms of tardive dyskinesia especially orofacial symptoms. Christina W. Slotemaa et al. conducted a single blind trail by including 12 patients treated with botulinum toxin A for 33 weeks resulting in non significant improvement of orofacial tardive dyskinesia symptoms. [54] one case report [55] and van Harten PN et al. reported that upon the repeated injection botulinum toxin A to the TD patients improvement of orofacial symptoms are observed. [56]

Calcium Channel Blockers: Calcium channel blockers are originally used to treat hypertension.but, some studies have been done to determine the efficacy of calcium channel blockers in tardive dyskinesia. Cates m et al. conducted a review to determine the beneficial effects of calcium channel blockers in tardive dyskinesia by including relevant case reports, open trails and controlled trails reporting on the efficacy of calcium channel blockers. positive findings are reported for nifedipine,verapamil and diltiazem among these drugs nifedipine is most efficaceous and diltiazem is least.hence calcium channel blockers should be considered as an useful therapy for tardive dyskinesia. [57] In one double blind placebo controlled cross over study verapamil (80mg/qid) and vitamin E (400iu/tid) are administerd to the TD patients resulting in the improvement of symptoms but the change associated with calcium channel blockers is less than the change associated with vitamin E. [58]

Donepezil: Donepezil is a cholinesterase inhibitor. Some studies have done to determine the efficacy of donepezil in tardive dyskinesia, addition of donepezil may effective in the treatment of tardive dyskinesia and these beneficial effects of donepezil supporting the cholinergic hypothesis. One case report suggested that involuntary movements lip and tongue

are controlled by donepezil [59]and Caroff SN conducted a open label trail by including 10 patients who received stable doses of antipsychotics treated with donepezil 5 to 10 mg/day for 6 weeks resulting in decreased AIMS scores significantly. Hence according to this study donepezil is effective in treating tardive dyskinesia. [60]

Melatonin: Melatonin is an endogenous hormone synthesized in the pineal gland and it has potent antioxidant action. Melatonin is beneficial in the treatment and prevention of tardive dyskinesia by attenuates dopamine activity in the striatum and dopamine release from the hypothalamus. [61, 62,63] Eyal shamir MD conducted a double blind placebo controlled cross over study by including 22 patients administered 10mg/day of melatonin for 6 weeks and assessed by AIMS score resulting in reduction of AIMS score is observed. [64]

Gabapentin: Gabapentin is an anticonvulsant and it was tried in several studies in order to determine its efficacy in treating tardive dyskinesia but only limited data is available. Harov mc conducted an open designed follow up study for one year in which 30 patients were included and treated with gabapentin and the results were evaluated by using the AIMS score. A statistically significant decrease in AIMS scores is observed. [65]

Levetiracetam: Levetiracetam is an anticonvulsant drug which is also effective in the treatment of tardive dyskinesia. The mechanism of its efficacy in treating tardive dyskinesia is unclear but it was expected to have a role in reducing the neuronal hyper synchrony in the basal ganglia. Woods SW conducted a double blind placebo controlled randomized study by including 50 anti-psychotic treated patients and given levetiracetam 500mg to 3000mg/day or placebo for 12 weeks and efficacy was assessed by using AIMS score and safety was assessed by using adverse event scale, psychiatric symptom rating scales, weight and hematologic tests. AIMS score reduction is spiked in treatment group (43.5%) than placebo group (18.7%).[66] Meco G et al. conducted a study by including 16 patients who are suffering from chronic psychosis associated with tardive dyskinesia and the treatment was started with a dose of 125 mg twice daily of levetiracetam and was mounted until the clinical effect is observed and results were assessed by using AIMS score, which revealed significant improvement. [67]

Ondansetran: Ondansetran is a selective serotonin 3 receptor antagonist and it was proved as safe and effective in controlling tardive dyskinesia, but with limited evidence. Pinkhas Sirota, M.D et al. conducted an open labelled trail on ondansetran by including 20 patients

suffering from schizophrenia associated with neuroleptics-induced tardive dyskinesia when given at a dose of 12 mg/day for 12 weeks which showed statistically significant improvement. [68]

Pyridoxine: Pyridoxine is the vitamin B6. The use of pyridoxine in tardive dyskinesia is supported by double blind cross over design. Vladimir Lerner, M.D., Ph. D conducted a double blind cross over design by including 15 patients with schizophrenia who were randomly assigned to treat with vitamin B6 or placebo for 4 weeks which was assessed by using extra pyramidal symptom rating scale and these ratings were significantly better in third week of treatment with pyridoxine than placebo. [69]

Quercetin: Quercetin is a naturally occurring bioflavonoid. Oxidative stress and lipid per-oxidation are involved in the pathophysiology of tardive dyskinesia. The chronic haloperidol treatment induces lipid per-oxidation and pulls down the glutathione levels in the forebrain, antioxidant defense enzymes, superoxide dismutase (SOD) and catalase. Naidu ps et al. suggested that Co-administration of quercetin with neuroleptics (25-100mg/kg) significantly reduced the lipid per-oxidation and restored the decreased glutathione levels and reversed decreased SOD levels. [70]

Naltrexone: Naltrexone is an opioid peptide encephalin and it is effective in treating of tardive dyskinesia when combined with the benzodiazepine (clonazepam). Wonodi, Ikwunga MD et al. conducted a 2 double-blind, placebo-controlled, randomized, crossover trials, and tested the efficacy of naltrexone alone (n = 9) and in combination with clonazepam (n = 14) in tardive dyskinesia patients. Naltrexone in combination with clonazepam was found to be more effective in treating tardive dyskinesia. [71]

Sodium Oxybate and Fish Oils: Very limited evidence was available which confirms the efficacy of sodium oxybate and fish oils in the treatment of tardive dyskinesia.

CONCLUSION

Tardive dyskinesia is a delayed onset side effect of the chronic use of the neuroleptics and it has no evidence based effective treatment. There were tons of studies performed as a trial and error process in order to have an effective treatment for tardive dyskinesia. According to the various studies performed, it was proven that the clozapine and the vitamin-E were found to be most effective in treating the tardive dyskinesia than other drugs , which were followed by

tetrabenazine, reserpine, clonazepam, sodium valproate, baclofen, vigabatrin. The less commonly used drugs in treating the tardive dyskinesia are amantidine, amino-acids, botulinum toxin, calcium channel blockers, donepezil, melatonin, gabapentin, levetiracetam, ondansetran, pyridoxine, quercetin, naltrexone, sodium oxybate and fish oils.

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