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REVIEW ARTICLE

DRUGS FOR SYMPTOMATIC TREATMENT OF HUNTINGTON'S DISEASE: A NEURO-DEGENERATIVE DISORDER

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ABSTRACT

Huntington's disease is a devastating inherited neurodegenerative disease characterized by progressive motor, cognitive, and psychiatric symptoms. Patients may present with any of these symptoms, and familiarity with the phenotype is therefore important. Chorea and loss of balance are early symptoms that patients notice, although families often notice cognitive or personality changes before this. Although no therapy is currently available to delay the onset of symptoms or prevent the progression of the disease, symptomatic treatment of patients with Huntington disease (HD) may improve the quality of life and prevent complications. As is the case with other neurological diseases, HD makes individuals more vulnerable to side effects from medications, particularly cognitive adverse effects. Symptomatic treatment for HD can be divided into drugs to treat the movement disorder and drugs to treat psychiatric or behavioral problems. Symptomatic treatment of Huntington's disease involves use of Dopamine antagonists, presynaptic dopamine depleters, Antidepressants, Tranquillizers, Anxiolytic Benzodiazepines, Anticonvulsants and Antibiotics. Several medications including baclofen, idebenone and vitamin E have studied in clinical trials with limited samples. This article reviews current therapeutic agents for treatment of the symptoms of Huntington's disease. The aim of present article is to provide in depth knowledge about symptomatic treatment and other therapies involved in the management of Huntington's disease.

Key words: Huntington's disease, Neurodegenerative, Symptomatic treatment, Antidepressants, Chorea.

INTRODUCTION:

Huntington's disease (HD) is an inherited disease of the central nervous system that usually has its onset between 30 and 50 years of age. The disease occurs in all racial groups but is most common in people of northern European origin. The mean age of onset of symptoms is 40 years, but juvenile onset (<20 years) and older onset (>70 years) forms are well recognized[1, 2]. The Huntington's disease Association (HDA) has records of 6161 adults with symptomatic Huntington's disease and 541 children with juvenile Huntington's disease (in England and Wales) at the time of writing. This is a conservative estimate of prevalence because it includes only those people in contact with the HDA, and it suggests that the true prevalence of the disease is higher than previously thought[3, 4].

COMMON SYMPTOMS OF HUNTINGTON'S DISEASE

1.Motor symptoms: Chorea, dystonia, loss of postural reflexes, bradykinesia, rigidity.

2.Cognitive symptoms: Disorganization as a result of difficulties with planning, initiating, and organizing thoughts, activities, and communication; perseveration; impulsivity; perceptual distortions; lack of insight; distractibility; difficulty in learning new information.

3.Psychiatric: Depression, obsessive-compulsive disorders, anxiety, irritability, apathy, hyper sexuality (uncommon), psychosis (uncommon).

4.Metabolic: Weight loss, sleep disturbance.

5.Others: Dysphasia (combination of motor and language difficulties), dysphagia (combination of motor problems, impulsivity, and distractibility)[5, 6].

DIAGNOSIS:

DNA analysis can be used to confirm the diagnosis. Tests are available to identify whether someone has the faulty gene. Genetic testing can diagnose Huntington's disease at every stage of the life cycle. There are three categories for testing such as: antenatal or prenatal, pre-symptomatic and confirmatory testing.

Antenatal or Prenatal Testing:

Either amniocentesis (a sample of fluid from around the fetus), or chorionic villus sampling (CVS)-a sample of fetal cells from the placenta will indicate whether the body has inherited the gene for Huntington's disease. Antenatal

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tests are carried out early in pregnancy on the unborn children of couples from families affected by Huntington's disease. They can be used to calculate the risk of that child going on to develop the disease in their adult life. Again, the implications of positive results are serious and couples need advice and support from a specialist doctor or counselor to help them in their decisions[7, 8].

Pre-symptomatic Testing:

These are available to the people who are at risk of inheriting Huntington's disease from a parent, but do not have symptoms and don't know whether or not they carry the gene. Pre-symptomatic tests are carried out in people who are not showing symptoms of Huntington's disease, but have a family history of it. The decision to take a test is a serious one: a positive result can be devastating since it tells the individual that they will one day become severely mentally ill. There are also issues surrounding testing when the individual parents have themselves not been tested, since a positive result indicates that one parent also has the faulty gene. Advice from a genetic counselor about the implications of taking the test is needed before going ahead[6, 9].

Confirmatory Testing:

This determines whether a person showing what appear to be the symptoms of Huntington's disease, actually has the disease. Neurological and psychological tests are also conducted to arrive at a conclusive diagnosis of Huntington's disease[1, 3, 10].

TREATMENTS AND DRUGS:

No treatments can alter the course of Huntington's disease. But medications can lessen some symptoms of movement and psychiatric disorders. And multiple interventions can help a person adapt to changes in his or her abilities for a certain amount of time. Medication management is likely to evolve over the course of the disease, depending on the overall treatment goals. Also, drugs to treat some symptoms may result in side effects that worsen other symptoms. Therefore, the treatment goals and plan will be regularly reviewed and updated[11].

Monoamine inhibitor:

Tetrabenazine (Xenazine)
Tetrabenazine is the first drug approved specifically to treat chorea associated with Huntington disease. Depletes neurotransmitter stores of dopamine, serotonin, and noradrenaline within nerve cells in the brain, thereby altering transmission of electric signals from the brain that control movement by reversibly inhibiting vesicular monoamine transporter 2 (VMAT2). Efficacy and safety established in a randomized, double-blind, placebo-controlled, multicenter study. Patients treated with tetrabenazine had significant improvement in chorea compared with those treated with placebo. Additional studies support this effect. It is indicated for chorea associated with Huntington disease[12].

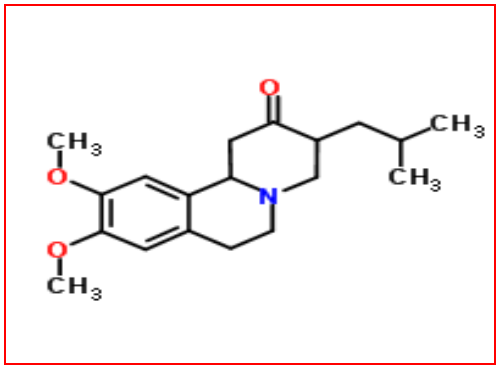

Figure 1: Structure of Tetrabenazine[13]

Anticonvulsant:

1. Valproic acid (Depakote, Depakene, Depacon)
Carboxylic acid commonly used as antiepileptic drug, mood stabilizer in mania, and prophylactic agent for migraine. When combined with sodium valproate in 1:1 molar relationship, called divalproex sodium. Mechanism by which valproate exerts its antiepileptic effects has not been established; its activity may be related to increased brain levels of GABA. No large clinical trials exist to support its use for hyperkinetic movement disorders, but it may be effective, as suggested by a few small studies in patients with chorea of different etiologies. Daily maximum dose of 2000 mg in divided doses (bid or tid) is enough to determine whether drug is going to be effective for individual patient[14].

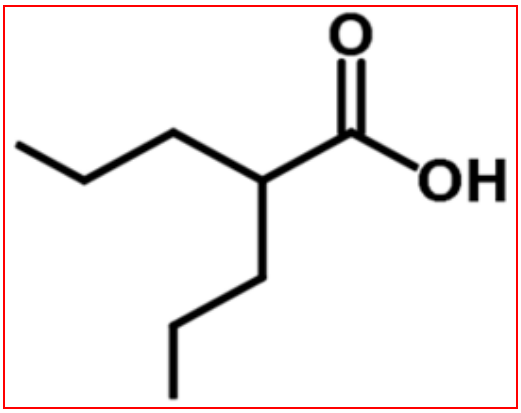

Figure 2: Structure of Valproic acid[15]

2.Clonazepam (Klonopin)

Clonazepam belongs to benzodiazepine class of drugs. It enhances activity of GABA, major inhibitory neurotransmitter in CNS. It is used commonly as antiepileptic drug. May be useful in treatment of chorea, but no large clinical trials exist to support its use. Does not induce Parkinsonism or carry risk of tardive syndromes, as neuroleptics do; therefore, an adequate trial with this medication is reasonable before using dopamine antagonists. Maximum daily dose of 2-4 mg divided bid/tid usually is enough to determine effectiveness for individual patient[14].

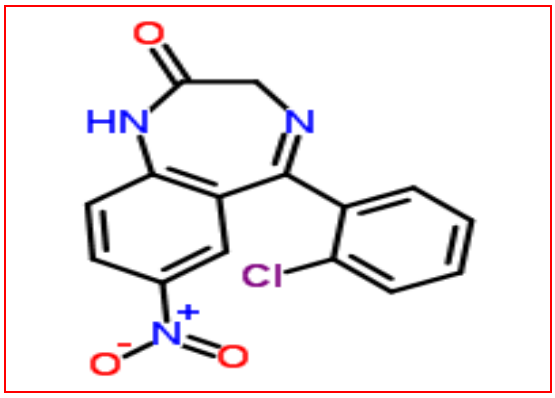

Figure 3: Structure of Clonazepam[16]

Antipsychotic agents:

These agents may improve choreic movements in patients.

1. Risperidone (Risperdal)

Antipsychotic agent is belongs to benzisoxazole derivatives. It is antagonist of type 2 dopamine and serotonin receptors[17].

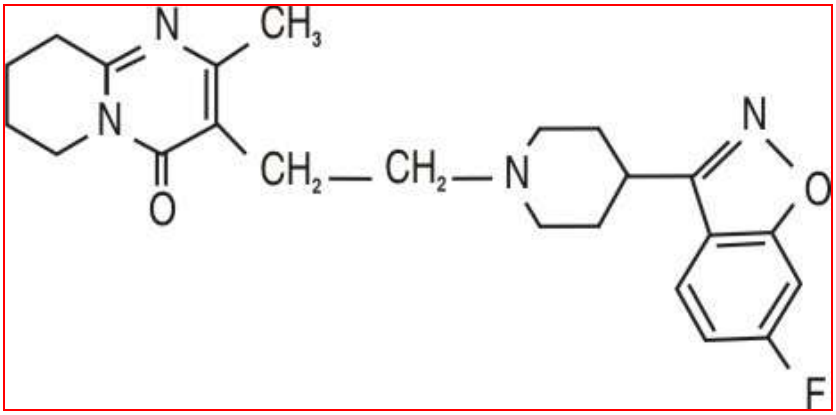

Figure 4: Structure of Risperidone[18]

2. Haloperidol (Haldol)

It is first of butyrophenone class of major tranquilizers. Typical neuroleptics, such as haloperidol, are potent dopamine-receptor antagonists and should be used only as last resort to treat chorea[17].

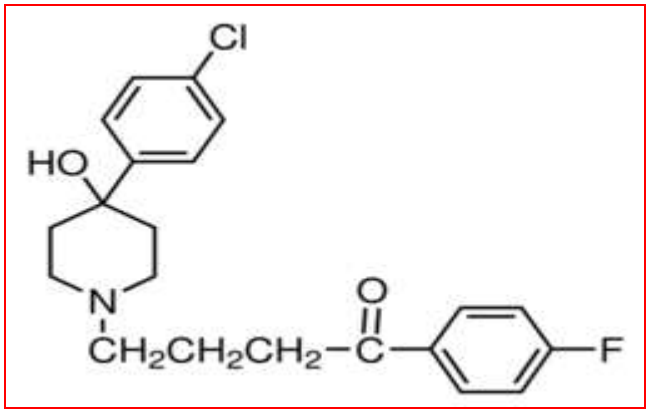

Figure 5: Structure of Haloperidol[19]

Rauwolfia alkaloids:

These agents may improve choreic movements in patients.

Reserpine

It is Dopamine-depleting agent. It is used in past to treat hypertension[20].

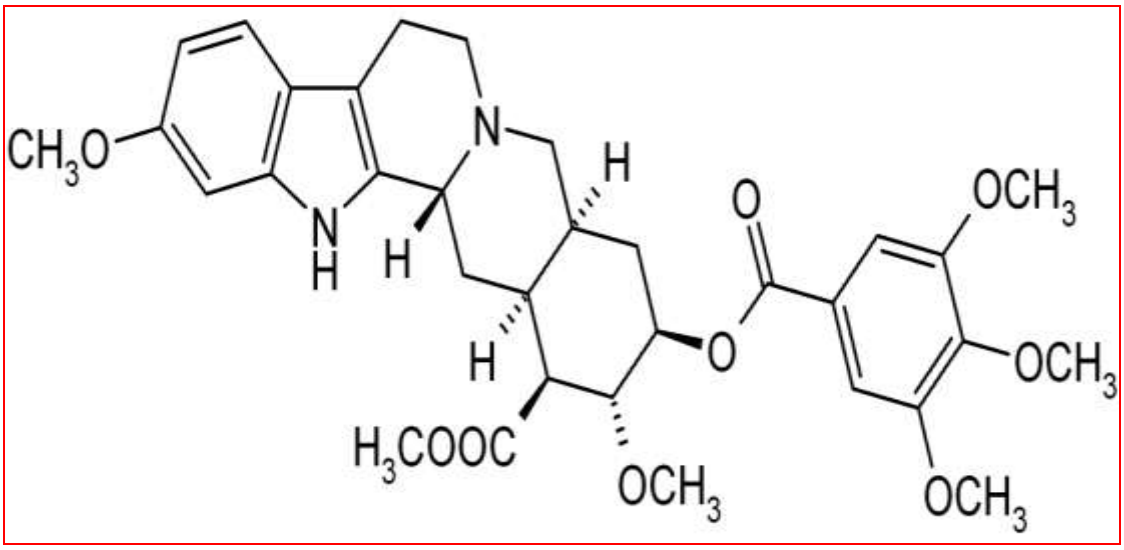

Figure 6: Structure of Reserpine[21]

Antidepressants:

Depression is relatively common in patients with HD and should be treated pharmacologically as soon as diagnosis of depression is made. Depression in patients with HD can be treated with the same agents used for treatment of depression of any other cause. SSRIs (Selective Serotonin Reuptake Inhibitors) may be used as first-line therapy because of their low adverse-effect profile, convenient dosing, and safety in the event of overdose. Other antidepressants can be used, including bupropion, venlafaxine, nefazodone, and the tricyclic antidepressants. Electroconvulsive therapy can be effective if an immediate intervention is required and in patients who do not respond to several good trials of medication.

Paroxetine (Paxil)

Selective Serotonin Reuptake Inhibitors that can be used once daily. Most patients should take it in morning because can be stimulating and may cause insomnia. If sedation occurs, drug should be taken at bedtime. A few patients develop sexual problems, such as decreased libido, anorgasmia, or ejaculatory delay[22].

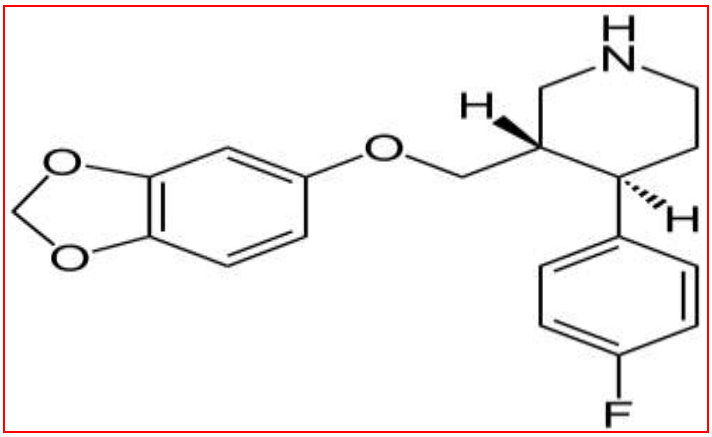

Figure 7: Structure of Paroxetine[23]

Table 1: Symptomatic Management of Movement Disorder in Huntington's Disease [2, 4, 7, 9]

Symptoms	Class of Drug	Drugs
Chorea	Atypical neuroleptics	Olanzapine, Risperidone
	Dopamine depleting agents	Tetrabenazine
	Older neuroleptics	Haloperidol, Sulpiride
Myoclonus	Anticonvulsant	Levetiracetam, Sodium valproate
Myoclonus, chorea, dystonia, rigidity, spasticity	Benzodiazepines	Clonazepam
Rigidity, spasticity	Skeletal muscle relaxants	Baclofen, Tizanidine
Rigidity	Amino acid precursor of dopamine	Levodopa
Bruxism, dystonia	Inhibits acetylcholine release at neuromuscular junction to cause muscle paralysis	Botulinum toxin

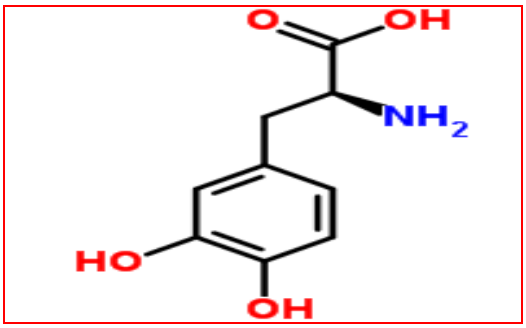

Figure 8: Structure of Levodopa[24]

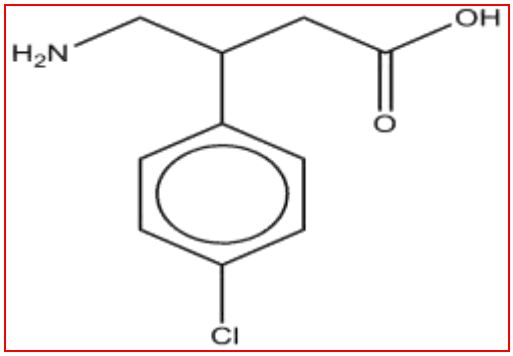

Figure 9: Structure of Baclofen[25]

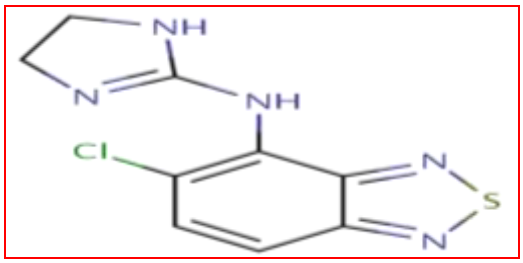

Figure 10: Structure of Tizanidine[26]

CONCLUSION:

Huntington's disease is neurodegenerative disorder characterized by midlife onset, involuntary movements, cognitive decline and behavioral disturbances. Managing the many facets of Huntington's disease can be challenging and is best served within multidisciplinary settings. We continue to learn about how to improve our services from our patients and their families. In the future treatments might be initiated in the premanifest phase, with the hope of delaying or halting the disease process itself. The goal of current research is to develop treatments that can prevent, retard or reverse neuronal cell death.

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