WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 8, 804-818. Review Article ISSN 2277– 7105

TREATMENT OF PARKINSON'S DISEASE

Diptesh T. Patil[1], Shaikh Sultana Gani Mohd*[1], Dr. Vanita Kanase[2], Dr. Pramila Yadav[3]

[1]Oriental College of Pharmacy[1], Sector 2, Behind Sanpada Railway Station, Sanpada West, Navi Mumbai, Maharashtra 400705.

[2]HOD Pharmacology[2], Oriental College of Pharmacy [1], Sector 2, Behind Sanpada Railway Station, Sanpada West, Navi Mumbai, Maharashtra 400705.

[3]Professor in Pharmacology[3], Dr. D. Y. Patil Medical College, Belapur, Navi Mumbai, Maharashtra 400614.

Article Received on
14 June 2015,

Revised on 05 July 2015,
Accepted on 25 July 2015

***Correspondence for Author**
Shaikh Sultana Gani Mohd
Oriental College of Pharmacy[1], Sector 2, Behind SanpadaRailway Station, Sanpada West, Navi Mumbai,Maharashtra 400705

ABSTRACT

Parkinson's disease [PD] is one of the most common neurodegenerative disorders. There have been significant recent advances in the understanding of the pathogenesis of the disease. There has also been a greater realization that the disorder may be associated with significant non-motor disturbances in addition to the more commonly recognized motor complications. There are many drugs like levodopa and carbidopa, ropinirole, pramipexole, rotigotine etc. and some MAO-B INHIBITOR like selegiline and rasagiline which are used in treatment of Parkinson's disease. Some COMT INHIBITOR and others drugs are also available and some herbs like turmeric, ginger, garlic etc. provides temporary relief from Parkinson's disease. There are two vaccines which are under development for the treatment of Parkinson's disease.

KEYWORD: Leodopa&Carbidopa, Tozadenant, Zonisamide, PD01A vaccine, PRX002 vaccine, Entacapone.

INTRODUCTION

A progressive disease of the nervous system marked by tremor, muscular rigidity, and slow, imprecise movement, chiefly affecting middle-aged and elderly people. It is associated with

degeneration of the basal ganglia of the brain and a deficiency of the neurotransmitter dopamine.[1]

In 2013 PD resulted in 103,000 deaths up from 44,000 deaths in 1990.[2]

The term Parkinsonism is used for a motor syndrome whose main symptoms are tremor at rest, stiffness, slowing of movement and postural instability. Parkinsonian syndromes can be divided into four subtypes according to their origin.

1. Primary or Idiopathic
2. Secondary[acquired] or Drug Induced
3. Hereditary parkinsonism, and
4. Parkinson plus syndromes or multiple system degeneration.[3]

Signs and symptoms[3]

1. Motor or Cardinal symptoms
2. Tremor
3. Rigidity
4. Bradykinesia and akinesia
5. Postural instability

1. Neuropsychiatric
2. Other motor symptoms

DRUG THERAPY

1. LEVODOPA AND CARBIDOPA

Striatal dopamine levels in symptomatic Parkinson's disease are decreased by 60 to 80%, striatal dopaminergic neurotransmission may be enhanced by exogenous supplementation of dopamine through administration of dopamine's precursor, levodopa. A small percentage of each levodopa dose crosses the blood-brain barrier and is decarboxylated to dopamine. This newly formed dopamine then is available to stimulate dopaminergic receptors, thus compensating for the depleted supply of endogenous dopamine. Striatal dopamine levels in symptomatic Parkinson's disease are decreased by 60 to 80%, striatal dopaminergic neurotransmission may be enhanced by exogenous supplementation of dopamine through administration of dopamine's precursor, levodopa. A small percentage of each levodopa dose crosses the blood-brain barrier and is decarboxylated to dopamine. This newly formed

dopamine then is available to stimulate dopaminergic receptors, thus compensating for the depleted supply of endogenous dopamine.[4]

Carbidopa inhibits aromatic-L-amino-acid decarboxylase [DOPA Decarboxylase or DDC], an enzyme important in the biosynthesis of L-tryptophan to serotonin and in the biosynthesis of L-DOPA to Dopamine [DA]. DDC exists both outside of [body periphery] and within the confines of the blood–brain barrier.[5]

Disadvantage of levodopa include things like hypotension [usually only associated with a very high dose], nausea, GI bleeding, disturbed respiration, hair loss, confusion, anxiety, insomnia, and in extreme cases even uncontrollable muscles.[4]

2. DOPAMINE AGONISTs

A dopamine agonist is a drug containing a molecule that binds to and activates dopamine receptors, similar to dopamine itself, thus compensating for low dopamine levels. Dopamine agonists are often used in younger patients, or in very early Parkinson's disease.

I. Ropinirole

Ropinirole acts as a D2, D3, and D4 dopamine receptor agonist with highest affinity for D2. It is weakly active at the 5-HT2, and α2 receptors and is said to have virtually no affinity for the 5-HT1, GABA, mAChRs, α1, and β-adrenoreceptors.[6]

II. Pramipexole

Pramipexole acts as a partial/full agonist at the following receptors.[7, 8]

- D_{2S} receptor [K_i = 3.9 nM; IA = 130%]
- D_{2L} receptor [K_i = 2.2 nM; IA = 70%]
- D_3 receptor [K_i = 0.5 nM; IA = 70%]
- D_4 receptor [K_i = 5.1 nM; IA = 42%]

III. Rotigotine

Rotigotine, a member of the dopamine agonist class of drugs, is delivered continuously through the skin [transdermal] using a silicone-based patch that is replaced every 24 hours. A dopamine agonist works by activating dopamine receptors in the body, mimicking the effect of the neurotransmitter dopamine.[9]

IV. Bromocriptine

Bromocriptine is a potent agonist at dopamine D2 receptors and various serotonin receptors.[10]

V. Pergolide

Pergolide functions as an agonist at the dopamine D2, D1 and serotonin 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, and 5-HT2C receptors. It may possess agonist activity at other dopamine receptor subtypes as well, similar to cabergoline. The weak agonist activity of pergolide at D1 receptors somewhat alters its clinical and side effect profile in the treatment of Parkinson's disease.[11]

3. MAO-B INHIBITOR

I. Selegiline

Selegiline is a selective inhibitor of MAO-B; MAO-B metabolizes dopamine and phenylethylamine.[12].Selegiline exhibits little therapeutic benefit when used independently, but enhances and prolongs the anti-Parkinson effects of levodopa.[12] Selegiline also inhibits CYP2A6 and can increase the effects of nicotine as a result.[13]

II. Rasagiline

The precise mechanisms of action of rasagiline is unknown. One mechanism is believed to be related to its MAO-B inhibitory activity, which causes an increase in extracellular levels of dopamine in the striatum. The elevated dopamine level and subsequent increased dopaminergic activity are likely to mediate rasagiline's beneficial effects seen in models of dopaminergic motor dysfunction.[14]

4. COMT INHIBITOR

I. Entacapone

The mechanism of action of entacapone is believed to be through its ability to inhibit COMT in peripheral tissues, altering the plasma pharmacokinetics of levodopa. When entacapone is given in conjunction with levodopa and an aromatic amino acid decarboxylase inhibitor, such as carbidopa, plasma levels of levodopa are greater and more sustained than after administration of levodopa and an aromatic amino acid decarboxylase inhibitor alone. It is believed that at a given frequency of levodopa administration, these more sustained plasma levels of levodopa result in more constant dopaminergic stimulation in the brain, leading to a greater reduction in the manifestations of parkinsonian syndrome.[15]

II. Tolcapone

Tolcapone binds to the catalytic center of COMT in both peripheral and central nervous systems with greater affinity than any of the three catecholamine, including levodopa.[16] It thereby prevents the 3-0-methylation of L-DOPA [3-hydroxy-L-tyrosine] by COMT which produces 3-O-methyldopa, a major metabolite that competes with levodopa to cross the blood-brain barrier. Thus, tolcapone improves the bioavailability and reduces the clearance of levodopa and subsequently dopamine from the central nervous system [CNS].[17]

5. OTHERS

I. Amantadine

Amantadine is a weak antagonist of the NMDA-type glutamate receptor,increases dopamine release, and blocks dopamine reuptake.[18] This makes it a weak therapy for Parkinson's disease. Although, as an antiparkinsonian, it can be used as monotherapy, or together with L-DOPA to treat L-DOPA-related motor fluctuations [i.e., shortening of L-DOPA duration of clinical effect, probably related to progressive neuronal loss] and L-DOPA-related dyskinesias [choreiform movements associated with long-term L-DOPA use, probably related to chronic pulsatile stimulation of dopamine receptors].[19]

II. Anticholinergic

i. Trihexyphenidyl [Benzhexol]

Trihexyphenidyl is a selective M1 muscarinic acetylcholine receptor antagonist. It is able to discriminate between the M1 [cortical or neuronal] and the peripheral muscarinic subtypes [cardiac and glandular]. Trihexyphenidyl partially blocks cholinergic activity in the CNS, which is responsible for the symptoms of Parkinson's disease. It is also thought to increase the availability of dopamine, a brain chemical that is critical in the initiation and smooth control of voluntary muscle movement.[20]

ii. Benzatropine

Benztropine is a selective M1 muscarinic acetylcholine receptor antagonist. It is able to discriminate between the M1 [cortical or neuronal] and the peripheral muscarinic subtypes [cardiac and glandular]. Benztropine partially blocks cholinergic activity in the CNS, which is responsible for the symptoms of Parkinson's disease. It is also thought to increase the availability of dopamine, a brain chemical that is critical in the initiation and smooth control of voluntary muscle movement.[21]

iii. Biperiden

Parkinsonism is thought to result from an imbalance between the excitatory [cholinergic] and inhibitory [dopaminergic] systems in the corpus striatum. The mechanism of action of centrally active anticholinergic drugs such as biperiden is considered to relate to competitive antagonism of acetylcholine at cholinergic receptors in the corpus striatum, which then restores the balance.[22]

NEW POTENTIAL DRUGS

1. A2A antagonists

1. Tozadenant [SYN115]

Tozadenant is in Phase 3 trials.[23]

Tozadenant is an orally administered, potent and selective inhibitor of the adenosine 2a [A2a] receptor that is being developed initially for the treatment of Parkinson's disease, but may also have utility in other CNS disorders. A2a receptors are expressed in high concentration in the striatum of the brain and there is an emerging body of evidence that they play an important role in regulating motor function. Tozadenant blocks the effect of endogenous adenosine at the A2a receptors, resulting in the potentiation of the effect of dopamine at the D2 receptor and inhibition of the effect of glutamate at the mGluR5 receptor. This enables restoration of motor function in Parkinson's disease patients without the induction of troublesome dyskinesias.[23]

2. Perampanel [E-2007]

The exact mechanism of action of perampanel in seizures is not yet determined, but it is known that perampanel decreases neuronal excitation by non-competitive ihibition of the AMPA receptor.[24]

3. Zonisamide

Zonisamide binds to sodium channels and voltage sensitive calcium channels, which suppresses neuronal depolarization and hyper synchronization. Zonisamide also inhibits carbonic anhydrase to a weaker extent, but such an effect is not thought to contribute substantially to the drug's anticonvulsant activity. [25]

4. Duodopa

Duodopa is a combination of levodopa and carbidopa [ratio 4:1] in a gel for continuous intestinal infusion in advanced Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia..[26]

5. Dopamine Agonists

I. Pardoprunox

Pardoprunox [SLV-308] is an antiparkinsonian drug currently under development by Solvay for the treatment of Parkinson's disease and as of March 2010 is in Phase III clinical trials.

Pardoprunox acts as a D2 and D3 receptor partial agonist and5-HT1A receptor full agonist.[27,28] It also binds to D4, α1-adrenergic, α2-adrenergic, and 5-HT7 receptors with lower affinity.[27,28] Relative to other dopaminergic antiparkinsonian agents, pardoprunox is thought to have significantly less of a propensity for inducing certain side effects like dyskinesia and psychosis.[28,29]

II. Aplindore

Aplindore [DAB-452] is a drug which acts as a partial agonist selective for the dopamine receptor D2.[30]

III. Lisuride

Lisuride is a dopamine and a partial agonist for several serotonin receptors. It is an antagonist at the serotonin 5-HT2B receptor.[31] It has a high affinity for the dopamine D2, D3 and D4 receptors, as well as serotonin 5-HT1A[32] and 5-HT2A/C receptors.[33]

6. COMT Inhibitor

Nebicapone is a novel catechol-O-methyltransferase inhibitor.Its action is similar to Tolcapone.[34]

7. MAO-B Inhibitor

Safinamide is a reversible and selective monoamine oxidase B inhibitor, reducing degradation of dopamine, and a glutamate release inhibitor.[35,36] It also seems to inhibit dopamine reuptake.[37] Additionally, safinamide blocks sodium and calcium channels.[36,38]

8. Other A2A antagonists[39,40,41,42]

I. Vipadenant [BIIA-014],

II. Fipamezole [JP-1730],
III. Lu AA4707,
IV. SCH-420814,
V. ATL-444,
VI. MSX-3,
VII. SCH-58261,
VIII. SCH-58412,
IX. SCH-58348,
X. SCH-58442,
XI. SCH-58416,
XII. VER-6623,
XIII. VER-6947,
XIV. VER-7835,
XV. ZM-241,
XVI. ZM-385

9. FP0011, a compound that reduces central glutamate levels, is now being studied in a Phase II trial.[43]

ROLE OF SURGERY

Brain surgery may be considered when drugs fail to control symptoms of Parkinson's disease or cause severe or disabling side effects. Surgery isn't a cure.

1. Deep brain stimulation [DBS]

DBS is a neurosurgical procedure involving the implantation of a medical device called a brain pacemaker, which sends electrical impulses, through implanted electrodes, to specific parts of the brain[brain nucleus] for the treatment of movement and affective disorders. DBS in select brain regions has provided therapeutic benefits for otherwise-treatment-resistant movement and affective disorders such as Parkinson's disease.[44]

2. Pallidotomy

In Parkinson's disease, a part of the brain called the globuspallidus is overactive. This causes a decrease in the activity of a different part of the brain that controls movement. In a pallidotomy, the surgeon destroys a tiny part of the globuspallidus by creating a scar. This

reduces the brain activity in that area, which may help relieve movement symptoms such as tremor and stiffness [rigidity].[45]

3. Thalamotomy

Thalamotomy is the precise destruction of a tiny area of the brain called the thalamus that controls some involuntary movements. Before surgery, detailed brain scans using a CT scan or MRI are done to identify the precise location for treatment. The person is awake during the surgery, but the scalp area where instruments are inserted is numbed with a local anesthetic. The surgeon inserts a hollow probe through a small hole drilled in the skull to the target location. An extremely cold substance, liquid nitrogen, is circulated inside the probe. The cold probe destroys the targeted brain tissue. The probe is then removed, and the wound is closed.[46]

AYURVEDIC TREATMENT

Parkinson's disease is known as "KAMPAVAAT" in Ayurveda.Ayurveda has a more holistic approach towards curing Parkinson's disease. This is a treatment in which the whole body will be treated. The whole premise of the ayurvedic approach is a natural Parkinson's treatment that would help the body become healthier while getting rid of the disease. The Ayurvedic treatment is based on the fact that most of the problems arise due to any imbalances in the tridosha [the biological humours in the body], which include the kapha, vata and the pitta.

Some of the Ayurvedic treatment for Parkinson's disease includes massaging. As a part of the Parkinson's treatment, a person will have to use extracts of important Ayurvedic plants such as didacordifolia or withania that are known to have an amazing effect on the nervous system, in their massage oils.

Parkinson's disease treatment is more successful when a combination of Ayurveda is used with Allopathy for a lot of reasons. The main one is the fact that Ayurveda combines a lot of important aspects of medication in order to deliver a full impact on the body- something western medicine has always ignored in. This is the reason why, when it comes to Parkinson's disease treatment, all the parts of the plant are used- including the seeds, roots, leaves, bark etc. This holistic approach would also minimize any side effects of using ayurvedic treatment for medicating Parkinson's disease. However, this does not mean that one should discount any benefit gained from allopathic medicine. It is simply to say that the effect of the

medication on the person's body and mind will be greater if Ayurveda is combined with Allopathic medication as well.[47]

HERB

1. **Turmeric Juice**[48]

- Neuron protective properties
- Removes the effect of oxidative stress
- Prevents clumping of proteins
- prevents cell death

2. **Ginger Juice**[49]

- Neurobiological & anti-inflammatory effects
- Keeps your memory sharp
- Release harmful toxins

3. **Garlic Juice**[50]

- High antioxidant capacity
- Increases antioxidant enzymes in brain cells
- Inhibits effects of neurotoxins
- Improves your digestion & immunity

4. **Lemon Juice**[51]

- Rich in Vitamins & Minerals
- Development of brain cells
- Powerful antioxidants to fight free radicals
- Natural Energizer

5. **Honey**[52]

- Prevent Cell Degradation
- Relieves symptoms of brain fog
- Reduces an oxidative stress

6. **Apple Cider Vinegar with Mother**[53]

- Boosts your general health
- Detoxifies Body
- Improves Blood Circulation

VACCINATION

1. PD01A

PD01A, the drug primes the body's immune system to destroy alpha-synuclein, a protein thought to trigger the disease by accumulating in the brain and disrupting dopamine production. Affiris, the company in Vienna, Austria, that developed the vaccine, says it is the first treatment to target the cause of the disease. "When it forms clumps in cells, alpha-synuclein disrupts normal levels of dopamine by locking it inside cells that produce it. It is also toxic, killing neurons and their connections.Most existing treatments only ease symptoms by boosting dopamine levels.[54]

2. PRX002

Treatment with PRX002 caused up to 96% mean reduction in free serum alpha-synuclein levels, which was found to be rapid and dose-dependent following the administration of a single dose. Overall results had high statistical significance. Moreover, PRX002 was safe and well tolerated among the patients.[55]

CONCLUSION

Parkinson's disease is a relatively common, progressive, movement disorder. It seems likely that the disorder has several, multifactorial causes in different groups of patients. Treatment is currently symptomatic, concentrating on alleviating the motor disability and reducing long-term motor complications of therapy. Although there is no cure, there are several management options for the early treatment of Parkinson’s disease. Conventional drug therapy is more effective and economically beneficial than new drug thearapies. As the disease progresses, further treatment options are available; however, the management of late-stage motor complications and non-motor symptoms remains particularly challenging and will benefit from further clinical research.

REFERENCE

1. http://www.oxforddictionaries.com/definition/english/Parkinson's-disease.
2. GBD 2013 Mortality and Causes of Death, Collaborators [17 December 2014]. "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study., 2013; 385: 117–71.
3. Jankovic J "Parkinson's disease: clinical features and diagnosis". *Journal of Neurology, Neurosurgery, and Psychiatry., 2008;* 79(4): 368–376.

4. Tanya Simuni and Howard Hurtig. "Levadopa: A Pharmacologic Miracle Four Decades. Later", in Parkinson's Disease: Diagnosis and Clinical Management [Google eBook]. Eds. Stewart A Factor and William J Weiner. Demos Medical Publishing, 2008
5. Gilbert JA, Frederick LM, Ames MM "The aromatic-L-amino acid decarboxylase inhibitor carbidopa is selectively cytotoxic to human pulmonary carcinoid and small cell lung carcinoma cells". *Clinical cancer research : an official journal of the American Association for Cancer Research., 2000;* 6(11): 4365–72.
6. Eden, R. J. et al. "Preclinical Pharmacology of Ropinirole [SK&F 101468-A] a Novel Dopamine D 2 Agonist".*Pharmacology Biochemistry & Behavior., 1991;* 38: 147–154.
7. Kvernmo T, Härtter S, Burger E "A review of the receptor-binding and pharmacokinetic properties of dopamine agonists". *Clinical Therapeutics., 2006;* 28(8): 1065–78. doi:10.1016/j.clinthera.2006.08.004. PMID 16982285.
8. ^ Jump up to:[a] [b] Newman-Tancredi A, Cussac D, Audinot V et al. "Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. II. Agonist and antagonist properties at subtypes of dopamine D[2]-like receptor and alpha[1]/alpha[2]-adrenoceptor". *The Journal of Pharmacology and Experimental Therapeutics., 2002;* 303(2): 805–14.
9. Scheller D, Ullmer C, Berkels R, Gwarek M, Lübbert H "The in vitro receptor profile of rotigotine: a new agent for the treatment of Parkinson's disease".*Naunyn-Schmiedeberg's Archives of Pharmacology., 2009;* 379(1): 73–86.
10. De Leeuw Van Weenen, J. E.; Parlevliet, E. T.; Maechler, P.; Havekes, L. M.; Romijn, J. A.; Ouwens, D. M.; Pijl, H.; Guigas, B. "The dopamine receptor D2 agonist bromocriptine inhibits glucose-stimulated insulin secretion by direct activation of the α2-adrenergic receptors in beta cells". *Biochemical Pharmacology., 2010;* **79**(12): 1827–36.
11. FDA Public Health Advisory: Pergolide [marketed as Permax]
12. http://web.archive.org/web/20070408111551/http://www.fda.gov/cder/drug/advisory/pergolide.htm.
13. Katzung, Bertram G. Basic & Clinical Pharmacology. 9th Edition. 2004. page 453. Lange Medical Books - McGraw Hill Publishers.
14. Siu, E. C.; Tyndale, R. F. "Selegiline is a mechanism-based inactivator of CYP2A6 inhibiting nicotine metabolism in humans and mice". *Journal of Pharmacology and Experimental Therapeutics., 2008;* 324(3): 992–9.
15. Youdim MB "Rasagiline: an anti-Parkinson drug with neuroprotective activity". *Expert Rev Neurother., 2003;* 3(6): 737–49.

16. "DrugBank: Entacapone [DB00494]". Drugbank.ca. Retrieved 2015-05-22
17. Deleu, D.; Northway, M. G.; Hanssens, Y. "Clinical Pharmacokinetic and Pharmacodynamic Properties of Drugs Used in the Treatment of Parkinsons Disease". *Clinical Pharmacokinetics., 2002;* 41(4): 261–309.
18. Jorga, K.; Fotteler, B.; Heizmann, P.; Gasser, R. "Metabolism and excretion of tolcapone, a novel inhibitor of catechol-O-methyltransferase". *British Journal of Clinical Pharmacology., 2001;* 48(4): 513–520.
19. Jasek, W, ed. [2007]. *Austria-Codex* [in German] [62nd ed.]. Vienna: ÖsterreichischerApothekerverlag. p. 3962.
20. Crosby, Niall J; Deane, Katherine; Clarke, Carl E [2003]. Clarke, Carl E, ed. "Amantadine in Parkinson's disease". *Cochrane Database of Systematic Reviews*.
21. Giachetti, A.; Giraldo, E.; Ladinsky, H.; Montagna, E. "Binding and functional profiles of the selective M1 muscarinic receptor antagonists trihexyphenidyl and dicyclomine". *British Journal of Pharmacology., 1986;* 89(1): 83–90.
22. "DrugBank: Benzatropine [DB00245]". Drugbank.ca. Retrieved 2015-05-22.
23. http://www.biotie.com/product-portfolio/syn115.aspx?sc_lang=en
24. Kornhuber J, Muehlbacher M, Trapp S, Pechmann S, Friedl A, Reichel M, Mühle C, Terfloth L, Groemer T, Spitzer G, Liedl K, Gulbins E, Tripal P "Identification of novel functional inhibitors of acid sphingomyelinase". *PLoS ONE., 2011;* **6**(8): e23852.
25. Rogawski MA, Hanada T. Preclinical pharmacology of perampanel, a selective non-competitive AMPA receptor antagonist. ActaNeurolScand., 2013; 127(197): 19–24.
26. Rossi, S, ed. [2013]. *Australian Medicines Handbook*[2013 ed.]. Adelaide: The Australian Medicines Handbook Unit Trust.
27. https://www.medicines.org.uk/emc/medicine/20786
28. Wolf WA "SLV-308. Solvay". *Current Opinion in Investigational Drugs [London, England : 2000;* 4(7): 878–82.
29. Glennon JC, Van Scharrenburg G, Ronken E et al. "In vitro characterization of SLV308 [7-[4-methyl-1-piperazinyl]-2[3H]-benzoxazolone, monohydrochloride]: a novel partial dopamine D2 and D3 receptor agonist and serotonin 5-HT1A receptor agonist". *Synapse., 2006;* 60(8): 599–608.
30. Gottwald MD, Aminoff MJ [July 2008]. "New frontiers in the pharmacological management of Parkinson's disease". *Drugs of Today [Barcelona, Spain : 1998;* 44(7): 531–45.

31. Heinrich JN, Brennan J, Lai MH, Sullivan K, Hornby G, Popiolek M, Jiang LX, Pausch MH, Stack G, Marquis KL, Andree TH. Aplindore [DAB-452], a high affinity selective dopamine D2 receptor partial agonist. *European Journal of Pharmacology*., 2006; 552(1-3): 36-45.
32. Hofmann C, Penner U, Dorow R, Pertz HH, Jähnichen S, Horowski R, Latté KP, Palla D, Schurad B "Lisuride, a dopamine receptor agonist with 5-HT2B receptor antagonist properties: absence of cardiac valvulopathy adverse drug reaction reports supports the concept of a crucial role for 5-HT2B receptor agonism in cardiac valvular fibrosis". *ClinNeuropharmacol., 2006;* 29(2): 80–6.
33. Marona-Lewicka D, Kurrasch-Orbaugh DM, Selken JR, Cumbay MG, Lisnicchia JG, Nichols DE "Re-evaluation of lisuride pharmacology: 5-hydroxytryptamine1A receptor-mediated behavioral effects overlap its other properties in rats".*Psychopharmacology [Berl.]., 2002;* 164(1): 93–107.
34. Egan CT, Herrick-Davis K, Miller K, Glennon RA, Teitler M "Agonist activity of LSD and lisuride at cloned 5HT2A and 5HT2C receptors".*Psychopharmacology [Berl.]., 1998;* 136(4): 409–14.
35. Maria JoãoBonifácio, P. NunoPalma,Luís Almeida andPatrícioSoares-da-Silva"Catechol-O-methyltransferase and Its Inhibitors in Parkinson's Disease"CNS Drug Reviews ,Volume 13, Issue 3, pages 352–379, Fall 2007
36. H. Spreitzer [14 April 2014]. "NeueWirkstoffe – Safinamid". *ÖsterreichischeApothekerzeitung* [in German] [8/2014]: 30.
37. Caccia, C; Maj, R; Calabresi, M; Maestroni, S; Faravelli, L; Curatolo, L; Salvati, P; Fariello, RG "Safinamide: From molecular targets to a new anti-Parkinson drug". *Neurology., 2006;* 67(7 Suppl 2): S18–23.
38. Merck Serono: *VielversprechendeDatenzurkognitivenWirkung von Safinamidbei Parkinson imFrühstadium.*[German] 8 June 2007.
39. Pevarello, P; Bonsignori, A; Caccia, C; Amici, R; Salvati, P; Fariello, RG; McArthur, RA; Varasi, M "Sodium channel activity and sigma binding of 2-aminopropanamide anticonvulsants". *Bioorganic & Medicinal Chemistry Letters., 1999;* 9(17): 2521–2524.
40. Hickey P, Stacy M. Adenosine A2A antagonists in Parkinson's disease: what's next? CurrNeurolNeurosci Rep., 2012; 12(4): 376-85.
41. Federico S, Spalluto G. Therapeutic potential of A2 and A3 adenosine receptor: a review of novel patented ligands. Expert OpinTher Pat., 2012; 22(4): 369-90

42. Kulisevsky J, Poyurovsky M. Adenosine A2A-receptor antagonism and pathophysiology of Parkinson's disease and drug-induced movement disorders. Eur Neurol., 2012; 67(1): 4-11.
43. Armentero MT, Pinna A, Ferré S, Lanciego JL, Müller CE, Franco R. Past, present and future of A[2A] adenosine receptor antagonists in the therapy of Parkinson's disease. PharmacolTher., 2011; 132(3): 280-99.
44. http://www.pdf.org/fall08_medications
45. Kringelbach ML, Jenkinson N, Owen SLF, Aziz TZ "Translational principles of deep brain stimulation". *Nature Reviews Neuroscience., 2007;* 8(8): 623–635.
46. http://www.webmd.com/parkinsons-disease/pallidotomy-posteroventral-pallidotomy-for-parkinsons-disease.
47. http://www.webmd.com/parkinsons-disease/thalamotomy-for-parkinsons-disease.
48. http://www.prokerala.com/health/parkinsons-disease/ayurveda-to-treat-parkinsons-disease.php.
49. http://herbaldaily.in/health_Benefits_haldi.html.
50. http://herbaldaily.in/health_Benefits_ginger.html.
51. http://herbaldaily.in/health_Benefits_garlic.html.
52. http://herbaldaily.in/health_Benefits_lemon.html.
53. http://herbaldaily.in/health_Benefits_honey.html.
54. http://herbaldaily.in/health_benefits_of_Apple_Cider_Vinegar.html
55. "World's first Parkinson's vaccine is trialled". New Scientist. 7 June 2012.
56. http://www.zacks.com/stock/news/168449/prothenas-prx002-positive-in-parkinsons-disease-study.