

A Review on Levodopa/Carbidopa drug for treatment of Parkinson's disease

Saurabh N. Bodkhe*¹, Omprasad R. Deshmukh², Prof.Pavan N. Folane³, Dr. R.H. Kale⁴, Dr.K.R.Biyani⁵

PRMSs Anuradha college of pharmacy Chikhli,
Dist-Buldhana (MS) India-443201

Abstract: Parkinson's Disease is a common movement disorder seen in neurological practice, but the diagnosis and management is challenging. The diagnosis is clinical and sometimes difficult, considering a large number of motor and non-motor symptoms in PD patients is difficult, as choices of drugs are limited and levodopa is the mainstay of treatment. However, Levodopa-induced dyskinesia (LID) is commonly seen in Parkinson's disease patients treated with levodopa, this side effect is usually encountered after a long duration of treatment, but occasionally. This may be seen after a few days or months of treatment. Levodopa a dopamine precursor is an effective and well tolerated dopamine replacement agents used to treat PD. The clinical use of levodopa may eventually be limited by the development of various treatment related complications, including response fluctuations and psychiatric s, poor bioavailability, narrow therapeutic window are all crucial for such fluctuations. Levodopa remains the most potent dopaminergic therapy for PD.

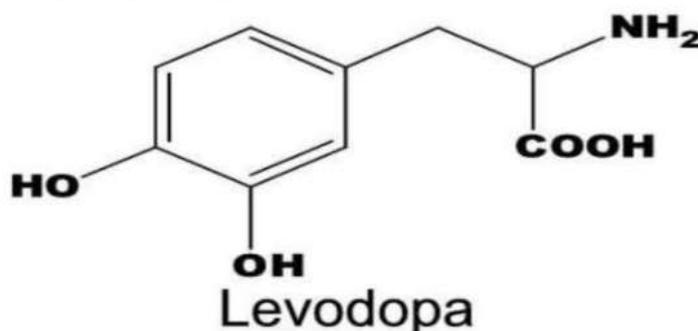
Keywords: Parkinson's disease, Levodopa/ Carbidopa, complication, Dyskinesia, motor fluctuation, Levodopa therapy.

1. INTRODUCTION:-

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder characterized by early prominent death of dopaminergic neurons in the substantia nigra pars compacta (aSyn) and wide spread presence of alpha synuclein (aSyn) an intracellular protein. Dopamine deficiency in the basal ganglia leads to classical Parkinsonian motor symptoms viz bradykinesia, tremor, rigidity and later postural instability. PD is also associated with non-motor symptoms, which may precede motor symptoms by more than a decade [1]. These non-motor symptoms in the later stages of PD. Although there have been remarkable advances in the medical and surgical treatment for PD. definitive disease modifying therapy is lacking. However, researches are hopeful that they will be able to identify the potential targets for disease modification [2]. With an ageing population, The management of PD is likely to prove an increasingly important and challenging aspect of medical practice for neurologists and general physicians. The diagnosis of PD remains essentially a clinical one, and it is important to recognize the early features together with symptoms and signs suggesting other causes of parkinsonism [3].

LD first synthesis dates backs in 1911, when the efforts of Kazimerz Funk, a polish passionate biochemist, paid with the identification of D,L-DOPA [4]. The pure left enantiomer, was isolated for the first time from the exotic bean plant vicia faba by Marcus guggeneheim, a swiss biochemist, who described it as an inactive compound despite the violent vomiting he experienced after having tried a 2.5g oral dose on himself, highlighting one of the most frequent systemic adverse events of LD in the Pre-AADC inhibitors [5]. Levodopa is a dopamine precursor and is a first line treatment that can restore motor function in PD patients [6]. The combination with levodopa and a dopa-decarboxylase inhibitor (DDCI), such as carbidopa or benserazide, reduces the peripheral DDC breakdown of levodopa and improves the proportion of peripheral levodopa crossing the blood brain barrier. There are some Levodopa modification strategies available to patients who begin to show symptoms of wearing off [7,8] some of these strategies include using lower and more frequent doses of Levodopa, changing to a treatment formulation that provides a more controlled release of levodopa or adding in a dopamine agonist [9]. Levodopa remains the most effective and well tolerated dopamine replacing agent [10], and contributes significantly to improvements in the quality of life of patients with PD [11].

1.1 History of Levodopa:- L-dopa, the naturally occurring isomer of the amino acid 3,4-dihydroxyphenylalanine, was first isolated in 1913 from legumes by Marcus Guggenheim [12] casimis funk had synthesized D,L- dopa in the laboratory two years prior to this at the welcome labs in London, England [13].



Almost 40 years later, Dale suggest its current name, dopamine for the compound synthesized earlier [14] both funk and Guggenheim considered the amino acid as a possible parent compound of adrenaline. The discovery by peter et al of an enzyme,

Dopa-decarboxylase, in mammalian tissue extracts that converted L-Dopa to the corresponding- biologically active amine, in 1938, represented a turning point in catecholamine research the discovery of the enzyme aromatic L-Amino acid decarboxylase, provided a mechanism for the formulation of dopamine in the brain from an exogenous source since L-Dopa, unlike dopamine itself, can cross the blood-brains- barrier . In 1942 Holtz demonstrated that the administration of L-dopa in laboratory animals and humans results in excretion of dopamine in the urine. He noticed that in humans, 50 mg L-Dopa intravenous caused tachycardia . Dopamine was isolated first in the adrenal medulla by Goodall, 1950 [15].

1.2 Mechanism of Levodopa Drug:-

combination with a DOPA decarboxylase inhibitor (DDCI), in this case carbidopa, which is very polar and cannot cross the blood brain barrier. However prevents peripheral conversion of Levodopa to dopamine and thereby reduces the unwanted peripheral side effects of Levodopa use of Carbidopa also increases the quantity of Levodopa Levodopa is converted to dopamine via the action of a naturally occurring enzymes called DOPA decarboxylase. This occurs both in the peripheral circulation and in the central nervous system after levodopa has crossed the blood brain barrier . Activation of central dopamine receptors improves the symptoms of Parkinson’s disease; however activation of peripheral dopamine receptors causes nausea and vomiting, for this reason levodopa is usually administered in in the bloodstream that is available to enter the brain.

Parkinson’s Disease Drugs

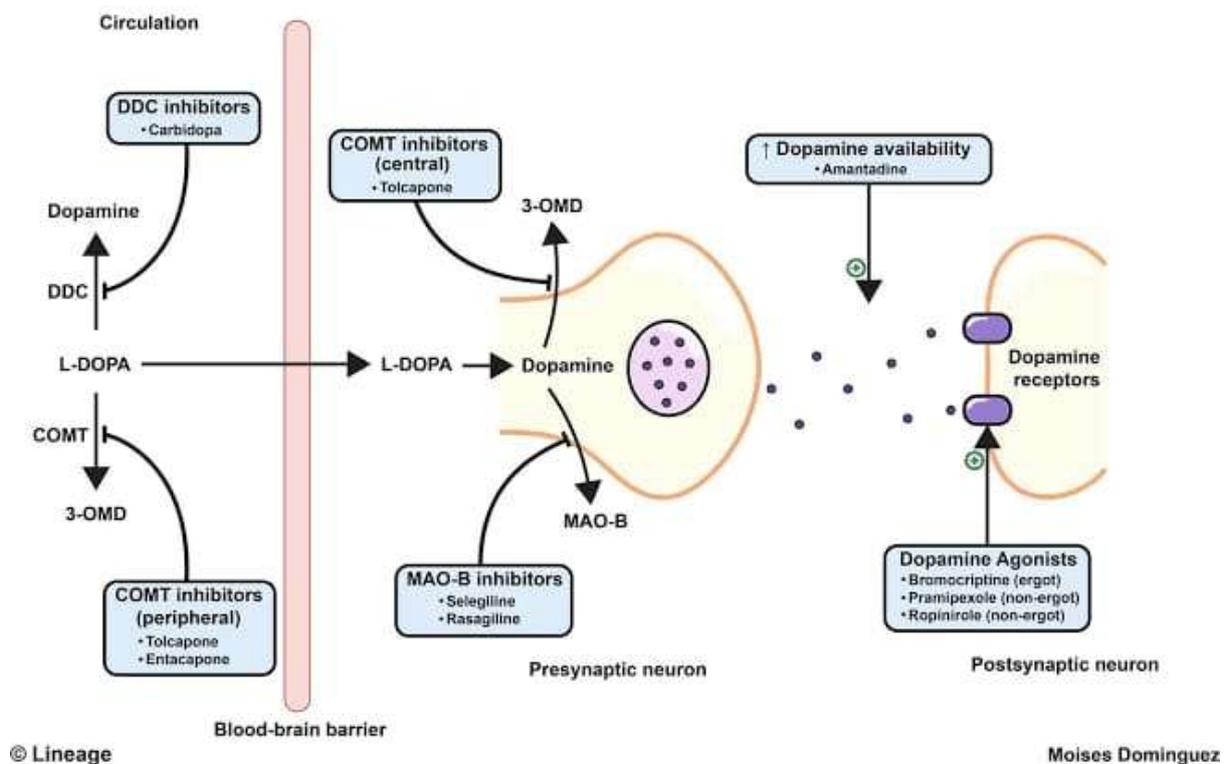


FIG 1: Parkinsons disease Drug

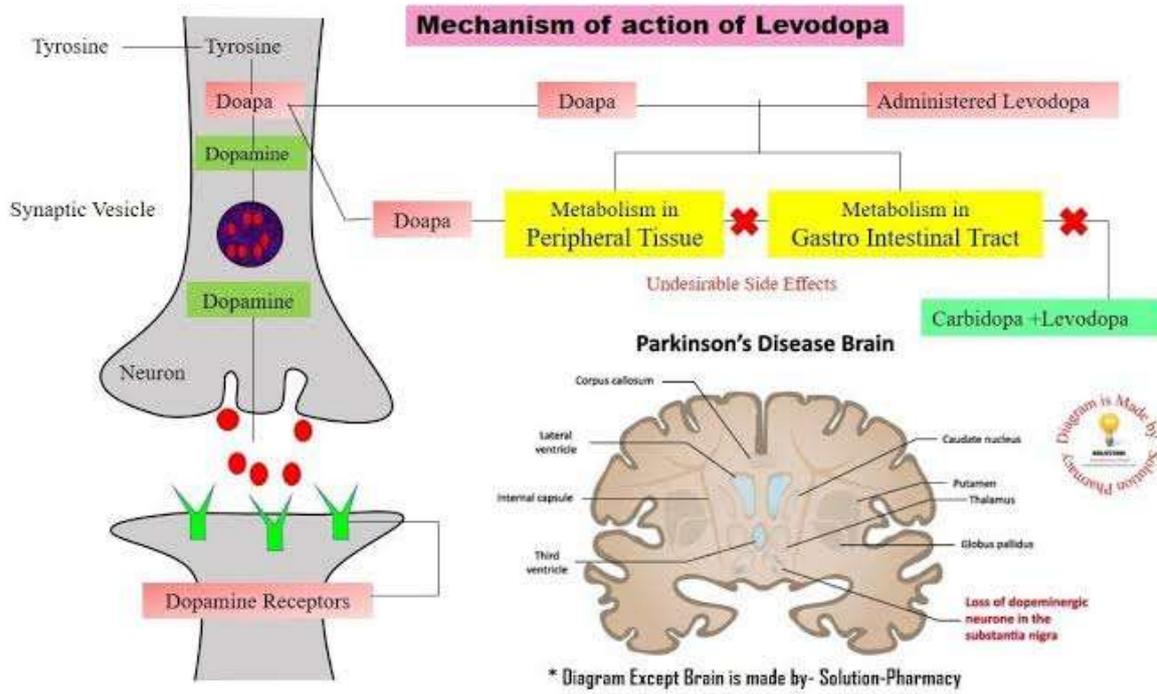


Fig 2: Mechanism of action of Levodopa

1.3 Pharmacology:-

Carbidopa inhibits aromatic-L-amino acid decarboxylase (DOPA decarboxylase or DDC) [16]. 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 and within the blood brain barrier. Carbidopa is used in the treatment of among other disease, Parkinson’s disease (PD), a condition characterised by death of dopaminergic neurons, in the substantia nigra [17]. Increase dopamine availability may increase the effectiveness of the remaining neurons and alleviate symptoms for a time. The use of Carbidopa seems counterintuitive in Parkinson’s disease (PD) in that it prevents DDC conversion of levodopa / L-DOPA gets metabolized peripherally to gets active metabolite dopamine before reaching the blood-brain-barrier. In Other words, carbidopa has no effect on brain DDC conversion of Levodopa/ L-DOPA to dopamine. Ultimately a greater proportion of the exogenously provided levodopa/ L-DOPA reaches the brain. Along with carbidopa, other DDC inhibitors are benserazide, difluromethylidopa and α -methylidopa.

Carbidopa

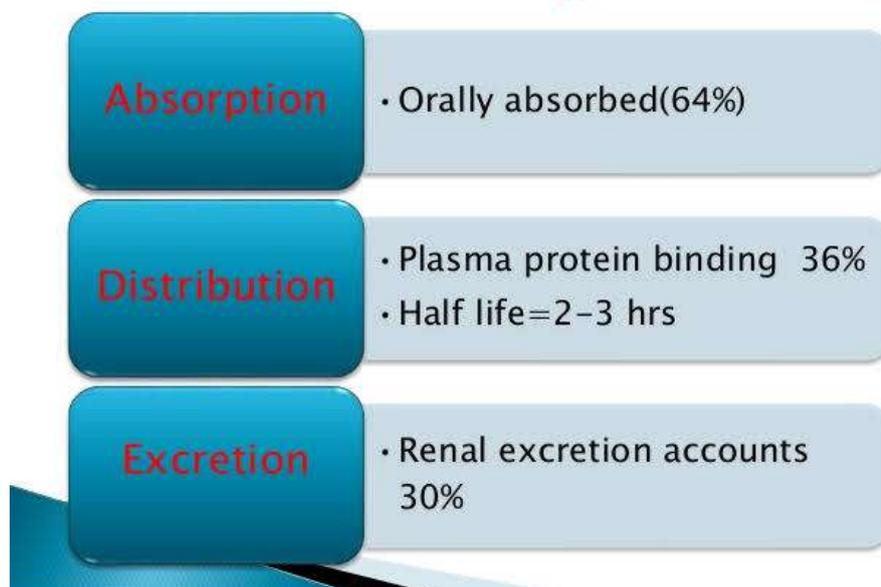


Fig 3: Pharmacokinetics of Carbidopa

2. THERAPEUTIC APPLICATION OF LEVODOPA:-

The major therapeutic application of levodopa is still revolves around its use in parkinsonism, Parkinson's plus syndrome and dopa-responsive dystonias. Clinical efficacy of levodopa varies in different subjects of symptoms. The classical motor symptoms of PD, bradykinesia and rigidity, usually respond well to levodopa. Nocturnal treatment is associated with dyskinesia and motor fluctuations. Dyskinesia are involuntarily movements that are mainly divided into peak-dose and biphasic dyskinesia. It is estimated that ~30%–50% of patients on levodopa therapy for more than 5 years experience dyskinesia [18]. The combination of carbidopa /Levodopa carries the brand name of Kinson, Sinemet, pharmacopeia and Atamet: whilw stalevo is a combination with entacapone, which enhances the bioavailability of Carbidopa and levodopa. Carbidopa is also used in Combination with 5-HTP, a naturally occurring amino acid which is Precursor to neurotransmitter serotonin and an intermediate in tryptophan metabolism, carbidopa, which is used in PD to Prevent conversion of levodopa to dopamine, prevents 5-HTP metabolism in liver and causes decreased level of Serotonin in the blood. In Europe 5-HTP is Prescribed with carbidopa to prevent the conversion of 5-HTP into serotonin until it reaches the brain.

3. LEVODOPA FORMULATION:-

1) Carbidopa /levodopa Immediate release tablets (Sinemet):-

*Available doses :-10/100mg,25/400mg,25/250mg

*Typical treatment Regimen :-150/1000mg of Levodopa total day (divided 3-4 times)

*Common side effects:- Low BP, Nauseas, Confusion, dyskinesia.

2) Carbidopa/ levodopa controlled release tablets (Sinemet CR*):-

*Available doses:- 25/100mg,50/200mg

*Typical treatment Regimen:-400/1600mg of levodopa in divided doses, depending on daily need.

*Common side effects:- Low BP, Nauseas, Confusion, Dyskinesia

3) Carbidopa/Levodopa orally disintegrating tablets (Parcopa):-

*Available Doses :-10/1 mg,25/100mg,25/250mg

*Typical Treatment Regimen :-150-1000 mg of Levodopa totally

*Common Side effects :- Low BP, Nausea, Confusion, Dyskinesia

4) Carbidopa/Levodopa enteral suspension (Duopa):-

*Available Doses :- 4.86/20 Per ml.

*Typical treatment Regimen :- Up to 2000mg of levodopa over 16 hours.

*Common side effects:- Low BP, Nausea, confusion, Dyskinesia.

5) Carbidopa /Levodopa External release capsules (Rytary):-

*Available doses :- 23.75/95mg,36.25/145mg,61.25/245mg

*Typical treatment Regimen :- 855-2340 mg of levodopa total daily dose

*Common side effects:- Low Bp, Nausea, confusion, Dyskinesia.

6) Carbidopa /levodopa/entacapone tablets (stalevo):-

*Available doses :- 12.5/50/200mg,18.75/75/200mg,31.25/125/200mg,50/200/200 mg

*Typical treatment Regimen :- 150-1600 mg of levodopa total daily dose, depending on the daily need maximum tablet per day

*Common side effect:-Nausea, Vomiting, Loss of appetite, confusion, light-headedness.

4. LEVODOPA THERAPY FOR PARKINSON'S DISEASE (PD):-

The efficacy of levodopa in PD has been widely recognised since its introduction over 40 years ago . Previous concerns that levodopa may have toxic effects on the brain have now been mostly discarded, and it is currently accepted that, at least in terms of toxicity, there is no reason to delay the initiation of LD [19]. The advent of LD in the late 1960s it has been routinely administered in combination with a dopa-decarboxylase inhibitor (DDCS) such as Carbidopa or bensarazide [20]. The bioavailability of CR-Levodopa formulation is, however, somewhat unpredictable and generally lower than that with conventional LD, thereby necessitating a 30% increase in dose [21] data regarding the degree of symptomatic control provided by each (R-Levodopa formulation is confliction: 2 studies reported better outcomes with CR formulations [22]. One study showed that CR formulation didn't increase on time without dyskinesia. One long term study [23] failed to demonstrate a significant decrease in rate of development of motor complications Another method for improving the bioavailability of plasma Levodopa and delivery to the brain is to inhibit peripheral metabolism of Levodopa Via the catechol-O-methyltransferase (COMT) pathway. A recent clinical trial in early stage untreated patients has shown that addition of entacapone to Levodopa/ Carbidopa therapy does not reduce the development of dyskinesias [24].Although another COMT inhibitor tolcapone, has been shown to be more effective than entacapone. It association with an increase risk of potentially fatal hepatotoxicity has limited its clinical use to patients who don't respond to entacapone [25], Although clinical potential is still being evaluated in a phase-3 clinical trial, Preliminary data suggest that pharmacokinetic profile of the novel COMT inhibitor opicapone may allow for a once-daily administration.

5. RECENT DEVELOPMENT IN TREATMENT WITH LEVODOPA:-

Once wearing off develops it can be ameliorated by smoothing out plasma levodopa levels and, furthermore, the hypothesis has been put forward that pulsatile-intermittent administration of levodopa may play a significant role in development of motor complication. According to strategies are being developed to obtain continuous drug delivery with Levodopa itself. The duodenal infusion of a water-soluble suspension of levodopa and carbidopa in methylcellulose, has found to be successful for achievement nearly stable plasma concentration of Levodopa [26].

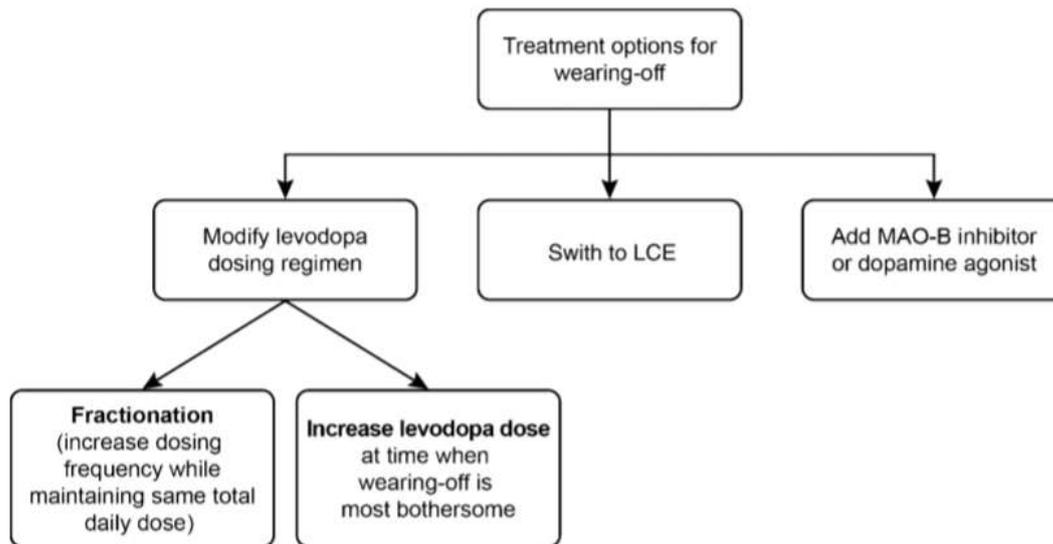


FIG 4: Pharmacological treatment options for patients with wearing off.

The Development for use in advanced in patients [27] the clinical benefits of LCIG infusion have been reported in multiple open label clinical trails on time with troublesome dyskinesias [28] A benefit on Certain non-motor symptoms [29]. Significant improvements in quality of life [30]. Preliminary results from controlled clinical trials, so far only presented in scientific meetings, also corroborate these finding [31] and suggest that LCGI infusion positively influences quality of life in this patient group [32], Vitamin B6 or Vitamin B12 deficiency and elevated plasma homocysteine levels. Which may lead to reversible encephalopathy, and axonal neuropathy, may occur more frequently than with oral formulation of the drug . An orally dissolved Carbidopa /Levodopa preparation was compared with regular levodopa/carbidopa . Patients were evaluated clinically using UPDRS score hand tapping task and Stride length at regular interval for 1hour and subjectively identified the onset of clinical response. Another study used the same design to evaluate potential difference between melevodopa hydrochloride/ LD and standard Levodopa/Carbidopa in 221 patients with regard to mean daily off time [33].

CONCLUSION:-

PD is one of the most common neurodegenerative disease affecting the ageing population and is associated with an increased mortality and mortality awareness of disease manifestation, the treatment and progressive long term course of the disease is necessary for optimal management of the case. PD remains a progressive disorder that eventually cause severe disability due to increasing severity of treatment resistant motor problems and Non- motor symptoms . 2 main aims animate the research in this field :- First to provide a more stable LD plasmatic Concentration and second, to find a suitable route through which LD could act almost spontaneously. Initiation in as first line therapy may achieve optimal outcomes in terms of patients function in early years of the disease. Around 10% of pathologically confirmed PD are Unresponsive to L-Dopa treatment and additional 12% have a modest response. An analysis of other modifying factor is required to further understand the reason for these observation. LD remains the most potent dopaminergic therapy for PD.

AUTHOR CONTRIBUTION:- The manuscript is conceptualised and data acquisition done by Saurabh Bodkhe & Omprasad Deshmukh. Critically reviewed the content and revised it.

REFERENCES:-

- 1) Olanow, C.W.; Stem, M.B.; Sethi, K. The scientific and clinical basis for the treatment of P.D. (2009). *Neurology*, 2009, 72(21)(suppl.4), 51-5136.
- 2) Rajput, A.H.; Biri, S. Epidemiology of P.D. *Parkinsonism Relat. Disord.*, 1997, 3(4), 175-186.
- 3) Jellinger, K.A. morphological substrates of parkinsonism with and without dementia a retrospective clinico-pathological study. *T. Neural Transm. suppl.*, 2007, 72(72), 91-104.
- 4) Hornykiewicz, O. L-DOPA; From a biologically inactive amino acid to a successful therapeutic agent. *Amino acid*, 2002, 23(1-3), 65-70.
- 5) Guggenheim, M. Dioxypheylalanin, eine neue Amino-saure aus vicia Faba, Hoppe Seyler's Z. *Physical. Chem.*, 1913, 88, 276-284.
- 6) P. A. Lewitt, Levodopa for the treatment of Parkinson's disease, *N Engl J. med* 359(2008), 2468-2476.
- 7) O. Rascol, D. J. Brooks, A. D. Karczyn, et al, A five year study of the incidence of dyskinesia in patients with early P.D who were treated with ropinirole or levodopa, *N, Engl J Med.* 342(2000), 1484-1491.
- 8) Parkinsons study group, pramipexole us levodopa as initial treatment for PD; a randomized controlled trail Parkinson Study Group, *JAMA*, 284 (2000), 1931-1938.
- 9) W. H. Derrel, E. Wolters, C. Sampaio, et al, pergolide versus levodopa PELMOPET study, *mov disord* 21 (2006), 343-353.
- 10) C. W. Olanow, J. A. Obeso, F. Stocchi, continuous dopamine-receptor treatment of P.D.: Scientific rationale and Clinical implication, *Lancet Neurol* 5(2006), 677-687.

- 11) C.W.Olanow, J.A. Obeso, F. Stocchi, Drug insight: Continuous dopaminergic stimulation in the treatment of P.D, *nat clin pract Neurol* 2 (2006), 382-392.
- 12) D.J. Brooks, m. Leinonen, m. kuoppamaki, et al, five year efficacy and safety of levodopa/DDCI and entacapone in patients with P.D, *J. Neural transm (Vienna)* 115 (2008), 843-849.
- 13) Guggenheim m. Dioxypheñilalolin, a new amino acid vicia faba. *Trubner*. 1913
- 14) Casimir. F. LxV-synthesis of dl-3:4-dihydroxyphenylalanine *J. chem Soc. trans* 1911;99:554-
- 15) Barger a, Dove HH. Chemical structure and sympatahomimetic action of amines. *J. Physiol.* 1910;41:19-59.
- 16) HDITz P, Credner K, Koepf W. The enzymatic formation of oxytyramine in the organism and the physiological significance of dopadecarboxylase. *Naunyn-Schmiedeberg's Archiv of pharmacology.* 1942;200:356-88.
- 17) Goodall. Mec. Dihydroxyphenylalanine and hydroxytyramine in mammalian superarenals. *Acta chem. Scand.* 1950;47:550.
- 18) Stocchi F, Zappia m, Dall Armin , et al (2010) melevodopa/ carbidopa effervescent formulation in the treatment of motor fluctuations in advanced PD, *mov Disord*, 25, 1881-1887.
- 19) Raab W, Gigg W. Concentration and distribution of 'encephalin' in the brain of humans and animals. *Proc Soc Exp Biol med.* 1951;76:97-100.
- 20) Cotzias GC, Van Woert MH, Schiffer LM. Ammatic amino acids and modification of Parkinsonism. *N. Engl J Med.* 1967;276:374-9.
- 21) Agid Y, Olanow CW, and mizuno y (2002) Levodopa : Why the controversy? *Lancet*; 360,575.
- 22) Papavasiliou Ps, Cotzias GC, Duby SC, steak AJ, Fehling C, and bell MA (1972) Levodopa in parkinsonism : potentiation of central effects with a peripheral inhibitor. *N Engl J med*, 286,8-14.
- 23) Sage . JI, and Mark MH (1994) pharmacokinetics of continuous release carbidopa/levodopa. *Clin Neuropharmacol*, 17 (suppl 2), 51-56.
- 24) Wolters EC, and Jesselaar HSM (1996) international (NK-VK) double-blind study of sinemet CR and standard sinemet (25/100) in 170 patients with fluctuating Parkinson's disease. 243,235-240.
- 25) Koller WC, Hutton. JJ Tolosa E and Capilladeo R (1999) Immediate-release and controlled-release carbidopa in PD: A 5 year randomized multicellular study *Carbidopa/ Levodopa study Group. Neurology* 53,1012-1019.
- 26) Stocchi F, Rascol o, kieburtz k, et al (2010) Initiating Levodopa/ Carbidopa therapy with and without entacapone in early PD: The STRIDE-PD study, *Ann neurol*, 68, 18-27.
- 27) Antonini. A, Abbruzzese G, barone p, et al. (2008). COMT. inhibition with tolcapone in the treatment algorithm of patients with PD: Relevance for motor and non-motor features. *Neuropsychiatr dis treat*, 4, 1-9.
- 28) Bredberg E, nillsson D, Johansson K, et al (1993) Intraduodenal infusion of water-based levodopa dispersion for optimisation of the therapeutic effect in severe PD. *EUR J Clin pharmacol*, 45, 117-122.
- 29) Nilsson. D, Nyholm D, and aquilonius sm (2001) Duodenal levodopa infusion in PD-long term, experience *Acta neurol scand*, 104, 343-348.
- 30) Syed n, Murphy J, Zimmerman J, et al (1998) Ten years experience eith enteral levodopa infusions for motor fluctuations in PD. *Mov disord*, 13, 336-338.
- 31) Nyholm D (2012) Duodopa (R) treatment for advanced PD. A review of efficacy and safety *parkinsonism relate disord*, 18, 916-929.
- 32) Kieburtz K, Antonini A, Olanow CW, et al (2012) randomized phase 3, double-blind, double-dummy study of levodopa-carbidopa intestinal gel in patients with advanced DD: functional and quality of life outcomes *mov. Disord*, 27, (Suppl 1), 385.
- 33) Urban PP, Wellach I, Faiss S, Layer P, et al (2010) subacute aonal neuropathy in PD with cobalamin and vitamin B6 deficiency under duodopa therapy. *Mov disord*, 25, 1748-1752.