Review Article

Parkinson's disease: A review on ONGENTYS®

Abstract:-

Aim: Parkinson's disease (PD) is an auto neuro-degenerative disease/disorder, mainly affects voluntary movements and behavioral functions in the elderliness. Previous studies narrated various aspects of Parkinson's disease but they could not explain the Parkinson's disease along with the Off-episode state and its management by using ongentys. In this review paper authors elaborately and comprehensively explained about Off-episode condition and its management by using Ongentys medicine.

Main body: In 25-50% population of Patient with PD it is found that they have developed OFF-Episode (Wearing-OFF) phenomenon in the first two years of treatment and after 10 years most of the patients were with off-episode condition. In this condition due to various known and unknown reasons medications used for PD are become ineffective between dose regimens that enable the symptoms of PD before next dose of Levodopa. To overcome this condition various medications are available in the market like- Entacapone, Tolcapone etc. A new approach has been developed for managing Off-episode problem in the PD patients i.e. Opicapone (Ongentys®). Opicapone is **COMT [Catechol-O-methyltransferase]** enzyme inhibitor, which prevents the degradation of Levodopa peripherally. COMT enzyme metabolizes Levodopa into *3-O-methyldopa* by methylation reaction peripherally as well as in the CNS region. Ongentys is used as a adjunctive with levodopa/carbidopa formulations and administered at bedtime only.

Conclusion: In this review authors mainly focus on the Ongentys® and its utilization in the management of off-episode state in PD patients. Authors also cover little bit about sign and symptoms, diagnostic tools, epidemiology of Parkinson's disease and drugs which may be used for the treatment of PD.

Keyword: Off- episode, Opicapone, COMT inhibitor, Adjunctive of Levodopa, Anti-Parkinsonian's agents

Introduction:-

A well known literature " An Essay on Shaking Palsy(1817)" was described by James Parkinson's on PD, hence the disease was named as Parkinson's disease. Further studies was carried out by Jean-Martin Charcot between 1868-1881 who demonstrated comprehensively the conception of PD. [1]

PD is a chronic neuro-degenerative disease delineated by- Tremor, rigidity, and bradykinesia along with wobbliness in some patient as the disease progresses. [2]

The death of dopaminergic neuronal cells in the Substantia-Nigra region of the mid-brain leads to deficiency of dopamine resulting in appearance of motor symptoms. Lewy bodies are developed in the neurons. [3]
Dopamine and acetylcholine are the neurotransmitter in our body ,Both neurotransmitter adjunctively play an important role to maintain body balance in all regular activities , Certain researches state that due to degeneration of dopaminergic neurons in PD patient acetylcholine level becomes elevated in basal ganglia and leads to demonstration of sign and symptoms of PD i.e. Tremor, Bradykinesia etc [4]

Although PD is idiopathic but, etiology of PD involves both genetic and environmental factors .
Environmental factors include exposure to herbicides(Paraquat), Pesticides(Rotenone) & Heavy metals(iron, copper, lead, alumminium and zinc). [5]
Drug induced Parkinsonism include-

- Phenothiazines(Chlorpromazine & Promazine etc)

- Butyrophenones (Haloperidol & beniperidol etc)
- Metoclopramide
- Tetrabenazine
- MPTP(1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), is a pro-drug to neurotoxin MPP^+, by destroying dopaminergic neurons it causes permanent symptoms of PD. [6]

Genetic factors – research indicates that around 5 to 10% of peoples with PD are known to genetically affected, in these patients PD is occurred due to mutation in one or several specific genes. It has been reported that autosomal dominant & autosomal recessive gene (11& 9 respectively) mutations have been embroiled in the development of PD. [7]

Sign and symptoms of PD

Most acknowledged symptoms in PD are Motor and non-motor symptoms include autonomic dysfunctioning such as- dysautonomia, neuropsychiatric and other are further described in table.1 [8]

SN.	Motor symptoms	Non-motor symptoms
1	Tremor	Neuropsychiatric disturbances- like-behavioral disorder. Cognition impairment(verbal, ocular and executive dysfunction) including dementia and punding.
2	Rigidity	Psychosis- hellucinations, delusion and associated delirium
3	Postural instability	Depression, apathy and anxiety
4	Bradykinesia	GI disturbances including constipations, dysphagia, silorrhea, gastroparesis
5	Freezing of gait	Genitourinary predicament- urinary incontinence and altered sexual functions like low libido.
6	Dystonia	Sweating- hyperhidrosis or hypohidrosis.

Table.1 Motor and non-motor symptoms

Epidemiology of Parkinson's disease

Certain longitudinal researches have been organized to identify the environmental and behavioral factors that are associated with the development of Parkinson's disease since 2006. [9]

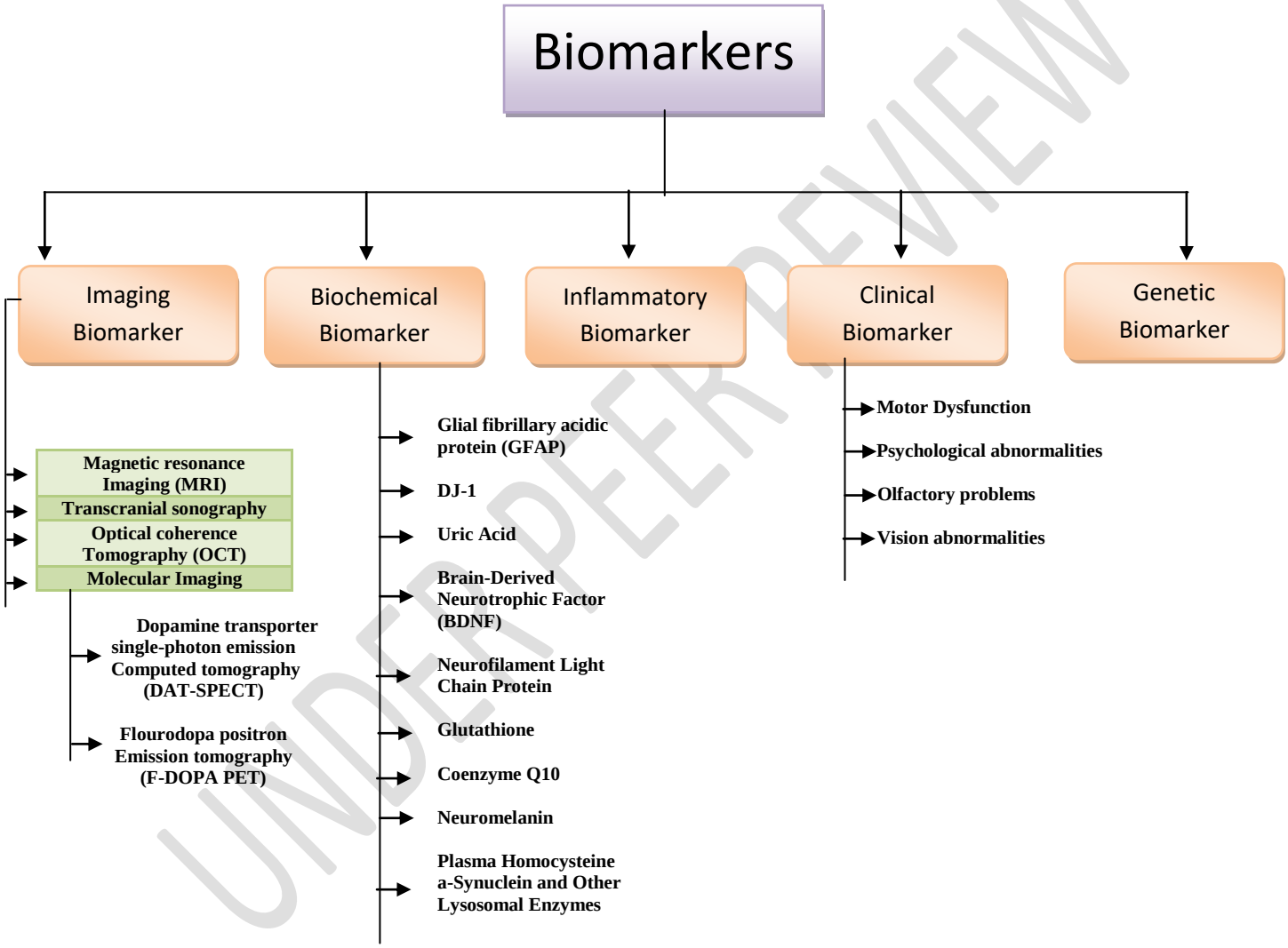
Higher risks of PD are associated with pesticidal exposure, dairy products consumption, melanoma history and brain injury, while reduced risks are associated with caffeine consumption, smoking, high uric acid concentration in serum , exercise and use of ibuprofen medicine. [9]

After Alzheimer's disease, PD is the second most common neurodegenerative disease in the world. The intensity of PD is low before 50 years of age but increases with the age very rapidly. Studies are carried out in higher income countries that state , in 100,000 peoples 14 person are affected with the age of 40-50 years , 160 with age of 65 years and most common in peoples having age 80 year or above. Male to female sex ratio was found to be around 1.3-2 which is around 0.95 in Asia.[9] More than 6 millions peoples have PD in the world. [10]

Diagnostic tools for PD

Despite of numerous efforts to point out the specific and sensitive biomarkers to diagnose PD is based on the clinical criteria which include- presence of motor features and non-motor features. [11]
Imaging:- includes MRI to look for alternative cause of symptoms such as vascular Parkinsonism. Computed tomography(specialized functional imaging test):- [1231]-FP-CIT single photon emission computed tomographyimaging and [18F] DOPA positron emission tomography imaging for the indication of dopamine deficiency in the striatum. [11]
Biomarkers help to detect the cerebrospinal fluid level, oxidative stress level and inflammation in the brain that would be helpful to prevent the PD at the earlier stage. Biomarkers indicate the state and progression of disease, effect of particular treatment that has been prescribed for the patient [11]

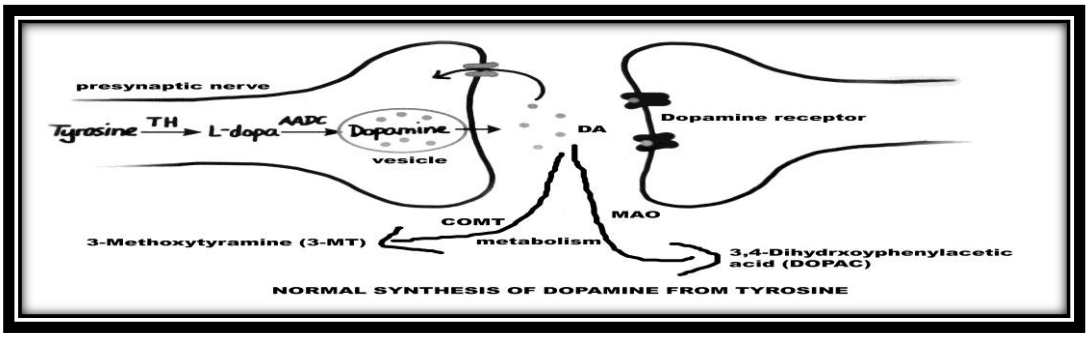
Some biomarker's approaches are enlisted below in the flow chart .1



Flow chart.1 biomarker's approaches

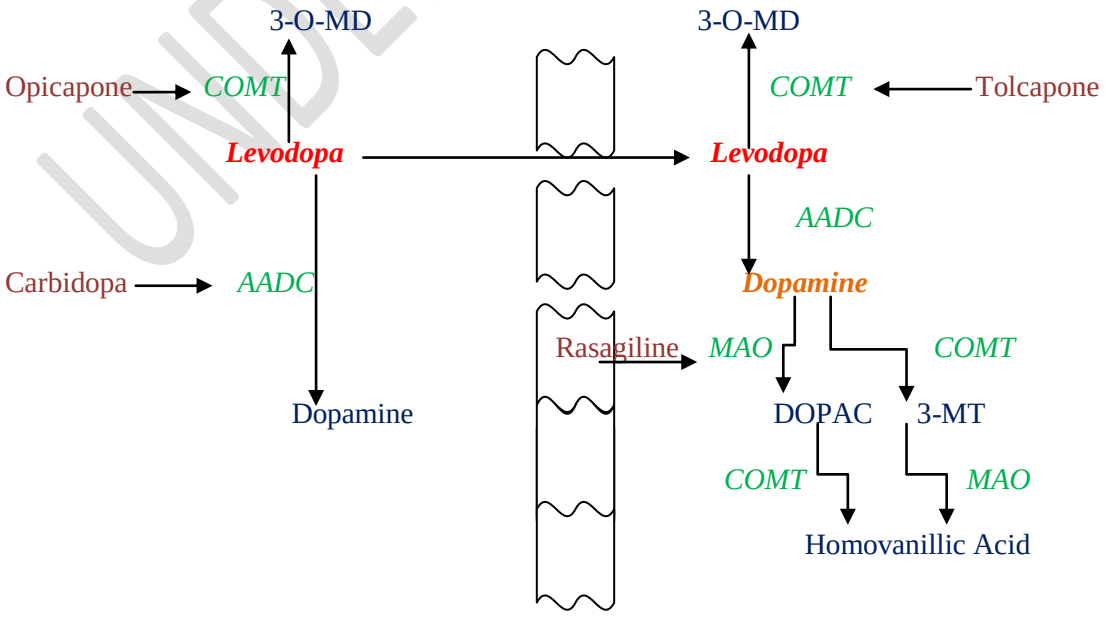
Drugs used in Parkinson's disease

Levodopa was the first synthetic, most effective and potent precursor of the dopamine which cross blood brain barrier (BBB) and reaches to CNS that stimulates to dopaminergic neurons to release more dopamine and control the symptoms of PD. Despite levodopa is the golden approach in the PD treatment but the transportation of levodopa to the CNS is not an easy task. Various enzymes are present in periphery and in CNS also that degrade the levodopa before reaching it at the desired site. like-



Picture.1 Normal synthesis of Dopamine from Tyrosine

1. **Aromatic L-amino acid decarboxylase (AADC)**
   This enzyme is mainly play a role in the conversion of *L-DOPA* into *Dopamine* by decarboxylation reaction in the CNS but when we administered the levodopa, AADC convert it into Dopamine peripherally that leads to nausea and vomiting. To overcome this retardation we can use Carbidopa or Benserazide with the levodopa. [12]
2. **Catechol-O-methyltransferase (COMT)**
   COMT enzyme converts *Dopamine* into *3-methoxytayramine* by methylation reaction in CNS ,when levodopa is administered into a patient *COMT* metabolized it into *3-O-methyldopa* peripherally as well as in CNS region before reaching to its desired site of action i.e. dopaminergic neuron. To overcome this limitation we can use COMT inhibitors adjacently with the levodopa like – Entacapone, tolcapone , opicapone. [12]
3. **Monoamine oxidase (MAO)**
   MAO enzyme do not affect the activity of levodopa but it metabolized the *Dopamine* into ***3,4-Dihydroxyphenylacetic acid*** *(DOPAC)* by the reaction called oxidative deamination, and reduce the level of dopamine at dopaminergic receptor site.MAO inhibitors are used to maintain the normal level of Dopamine in CNS as monotherapy or combined therapy with levodopa. MAO inhibitors are- Selegiline, Rasagiline, isocarboxazid, phenelzine,tranylcypromine . [13]



Dopamine agonists	Levodopa /Carbidopa preparations	COMT inhibitors	MAO-B Inhibitors	Anti-cholinergic	Miscellaneous

Periphery **BBB** **CNS**

Flow diagram.1. [14]
Transportation of levodopa from periphery to CNS

Along with levodopa there are various therapeutic agent which help to maintain the normal physiology during complications of PD. Drugs are categorized as follows-

1.Pramipexole (Immediate-release -0.125 mg-TD ,& extend-release 0.375 mg-OD) **ADRs-** orthostatic hypotension, nausea, dizziness ,sleepiness**.** 2.Ropinirole (Immediate-release -0.25 mg-TD ,& extend-release 2 mg-OD) **ADRs-** orthostatic hypotension, nausea, dizziness ,sleepiness**.** 3.Rotigotine (Patch-2mg) **ADRs-** orthostatic hypotension, dizziness, reactions at site of application. 4.Apomorphine (Injection-MDU) **ADRs-** orthostatic hypotension, dizziness, reactions at site of application.	1.Standard formulation (300-1000 mg/day) **ADRs-** Dyskinesia, nausea, chest pain, cardiac irregularities, vomiting, mouth dryness. 2.Extend release (855-2205 mg/day) **ADRs-** Dyskinesia, nausea, dizziness, insomnia, headache, sweating, salivation. 3.Gel formulation(intestinal infusion-600-1800 mg/day) **ADRs-** Dizziness, nausea, vomiting, trouble, sleeping, headache. 4.Inhalational powder (42-84mg/day) **ADRs-** Nausea, headache, cough, dyskinesia.	1.Entacapone (200 mg with each dose of levodopa) **ADRs-** Dyskinesia, dizziness, nausea, vomiting, diarrhoea, hallucination, drowsiness, dry mouth, abdominal pain, orange urine . 2.Opicapone (50 mg- ON) **ADRs-** Dyskinesia 3.Tolcapone (100 mg-TD) **ADRs-** Dyskinesia, dizziness, nausea, vomiting, diarrhoea, hallucination, drowsiness, orange urine .	1.Selegiline (5 mg-BD) **ADRs-**Dizziness, drowsiness, nausea, weight Loss. 2.Rasagiline (1 mg-OM) **ADRs-**Dizziness, drowsiness, heartburn, Nausea. 3.Safinamide (50mg-OD) **ADRs-**Dizziness, drowsiness 4.Zonisamide (25-200 mg/day) **ADRs-**Sleepiness, loss of appetite.	1.Trihexyphenidyl (2-8 mg/day) **ADRs-**Cognitive impairment, dry mouth, blurring of vision, urinary retention. 2. Benztropine (2-8 mg/day) **ADRs-**Cognitive impairment, dry mouth, blurring of vision, urinary retention.	1.Amantadine (100-300mg/day) **ADRs-**Dizziness, hallucination, nausea, confusion, myoclonus, livedo reticularis, leg swelling. 2.Istradefylline (20 mg/day) **ADRs-** Involuntary muscle movements, dizziness, constipation, nausea, hallucination, insomnia. **3.**Clozapine (12.5-25 mg -ON) **ADRs-**Sleepiness, dizziness, tachycardia, constipation, orthostatic hypotension, sialorrhea

General medications used for Parkinson's disease .Table.2 [10, 15]

Table 3 : Plant-derived extract for Parkinson's Disease:-

Extract	Activity profile
SAFFRON **(*Crocus sativus L.*)**	Neuro-protective activity by- *anti-inflammatory, antioxidant and immuno-regulatory pathways.*
TURMERIC **(*Curcuma longa*)**	Neuroprotective effect
CANNABINOIDS **(*Cannabis sativa*)**	Neuro-protective effect
RESVERATROL **(3,5,4′-trihydroxytrans-stilbene)**	Neuroprotective effect
POLYGONUM MULTIFLORUM **(*Fallopia multiflora*)**	Neuro-protective effect
GINKGO **(*Ginkgo biloba*)**	Neuro-protective effect
GREEN/BLACK TEA **(*Camellia sinensis*)**	Neuro-protective effect
ATREMORINE **(*Vicia fava*)**	Neuro-protective effect

Table.3 [16]

OFF/ON-episode phenomenon in PD:-

It is evident that the gold standard treatment for PD is Levodopa often combined with carbidopa to increase the efficiency of the prior which results in relief from the symptoms of PD. As the medication shows the therapeutic effect gradually, most of the population withstand the above treatment and begins to experience OFF episodes once their symptoms return or worsen. [17]

What is the OFF/ON phenomenon?

The OFF/ON phenomenon is a repercussion of sustained levodopa treatment in patient with PD.

In case of ON episode- L-dopa is functioning effectively and symptoms refine whereas in case of an OFF episode unfortunately the L-dopa isn't effective and the symptoms returns or worsen with increased anxiety and depression. [17]

A review found that in OFF episodes 25-50% patients with PD developed OFF episodes within two years of beginning of L-dopa therapy and after 10 years most of the patient had OFF episode state. OFF episode may be in predictable or unpredictable pattern, gradually or suddenly, affects different peoples in different ways . [17]

In a survey it is found that OFF episodes were linked to reduced life quality of people with PD. [17]

Causes for Off-episode state:-

Exact cause for Off-episode phenomenon is unrevealed, more studies are require to know about etiology of this complicated condition. [14]

But certain researches state that PD is progressive neurodegenerative disease which depletes Dopaminergic neurons gradually and due to loss of dopaminergic neurons effect of antiparkinsonian's agents declines gradually in PD patient. Different causes are associated with different types of Off-time phenomenon. [14]

- **Wearing-OFF:-** Levodopa half life is changed and symptoms are appeared more frequently in between the dose interval. Half life may be changed due to hyper-reactivity of enzymes present in both peripheral and CNS region. [14]

- **Delayed-ON:-** Delayed gastric emptying time causes abnormal intestinal absorption of the drug that leads to delayed effect of the medicine. [14]

- **Random ON-OFF:-** Dopamine receptor down-regulation(internalization) leads to change in pharmacodynamic properties of the drug. [14]

- **Dose failure or No-ON:-** Delayed gastric emptying time or various enzymatic reaction in peripheral region causes hindrance in the transport of drug to the CNS which resulting dose failure and complications in symptoms control. [14]

How to avoid or treat or prevent OFF-episodes

Patients should inform to doctor when he start to experience abnormal effect of medications prescribed for PD that doctor can take an appropriate action at the appropriate time. Various steps are included to avoid or manage the Off-episodes in PD patient.

1. **Always intake lower therapeutic dose:-** High dose of Levodopa more frequently develop Off-episodes and create complications in PD patient. To avoid, doctors always prescribe minimum therapeutic dose of levodopa. [14]
2. **Adjust dose or oral formulation of Levodopa/Carbidopa:-** At the initial stage of OFF-episodes doctor may prescribe more or lower dose or extend release formulation rather than a fast acting formulation of the levodopa. [17]
3. **Prescribe non-oral Levodopa/Carbidopa preparations:-** Inhalational preparation of levodopa or enteral formulations are prescribed by the doctor. In enteral delivery Levodopa/Carbidopa is continuously infused through a tube in the intestinal tract.[17]
4. **Use of adjunct medications:-** Along with levodopa adjunctive drugs are prescribed which helps to enhance the efficacy of the given dose. Adjunctive medications may include- MAO inhibitors , COMT-inhibitors, AADC- inhibitors. [17]
5. **Recommendation of dopamine agonists:-** These medications are come under the rescue medicine category for PD patients. Used when Off-episode is completely developed and quick relief is required**.** e.g.-sublingual Apomorphine. [17]
6. **Deep brain stimulation(DBS) therapy:-** in some cases doctor recommends DBS,in this surgeon implants electrodes in the brain and a pulse generator in the chest or abdominal region. This helps to maintain symptoms of PD. [14]

7. **Exercise** :- exercise is also helpful to manage the off-episodes state in PD patients. [18]

ONGENTYS®:-

General description of drug:-

IUPAC Name :-

2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol3-yl)-4,6-dimethylpyridine-1-oxide.[20]

Molecular formula:- C15H10Cl2N4O6

Molecular weight :- 413.17

Trade name:- ONGENTYS

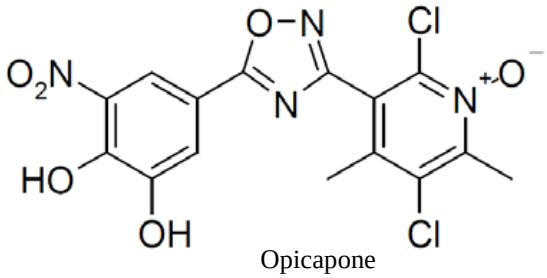
Route of administration:- Oral; Cap 25mg or 50mg

Protein binding:- 99.9%

Duration of action:- >24 hrs

Solubility :- limited aqueous solubility

Physical characteristics:- Crystalline solid / yellow powder. [19]



Opicapone

Objective:-

COMT is the major metabolized enzyme for the Dopamine as well as Levodopa peripherally and in CNS, ONGENTYS inhibit COMT activity peripherally. ONGENTYS is mainly prescribed for the management of OFF-episode state. Opicapone is third generation selective and reversible inhibitor. [19, 20]

Pharmacology:-

- ***Pharmacokinetic :-***

  - **Absorption:- Opicapone** is quickly absorbed from the gut ,on single dose administration of 50 mg of ONGENTYS T_{max} value was about 2hours(1-4 hrs). food interaction affect the absorption, intake with moderate fatty food may lead to reduction in C_{max} about 62% and mean overall plasma exposure decreased upto 31%, Hence doctors inform to patient that take before or after 1 hour of taking meal.[19]
  - **Distribution**:- plasma protein binding is high> 99% which demonstrate zero-order kinetics.
  - **Metabolism :-** Metabolized mainly by the Sulphation in the liver, other metabolic pathway may be glucoronidation , methylation, reduction and glutathione conjugation. [19]
  - **Elimination:-** elimination half-life is about 1-2 hrs and when 100 mg dose administered to healthy volunteer – about 70% (22% unchanged) recovered from feces ,20% from exhalation and 5% in urination (< 1% unchanged). [19]

Factors affecting pharmacokinetic of opicapone:-

- **Populations with specificity:-** No clinically significant differences were observed on the basis of age, sex, race in the pharmacokinetic of opicapone. [19]
- **Renal impairment:-** Studies are carried out on the subjects with mild to moderate renal impairment, no clinically significant differences were observed in the pharmacokinetic of opicapone. Studies for severe renal impairment could not be carried out. [19]
- **Hepatic impairment:-** studies were carried out on the subjects with mild and moderate liver problems, subjects with mild hepatic impairment have AUC increased by 35%which is not clinically significant difference in pharmacokinetic, subjects with moderate hepatic impairment have AUC increased by 84% which is clinically significant difference in pharmacokinetic of opicapone , hence dosing

adjustment is required for patients with moderate hepatic impairments. Hence doctor always prescribe 25 mg of opicapone instead of 50mg. patients with severe hepatic impairment were not studied with ONGENTYS. [19]

- **Drug-drug interaction:-** Not considerable differences in pharmacokinetic were observed of opicapone when administered with- Quinidine, acetaminophen, rasagiline, warfarin, repagilinide, selegiline, pramipexole, ropinirole, amantadine. [19]

➢ ***Pharmacodynamic:-***

- **Mechanism of action:-** once a day administration of 50mg dose causes inhibition of COMT (*catechol-O-methyltransferase*)enzyme upto 84% and maintain >65% for 24 hours. Inhibition of COMT enzyme activity prevent metabolism of Levodopa in the periphery and helps to transport the levodopa into CNS region(*see flow diagram.1*) . After reaching to CNS levodopa elevate the level of Dopamine in the CNS resulting in relieve PD symptoms. C_{max} and AUC of levodopa/carbidopa administered every four hours is increased about 43to 44% and 62 to 94% respectively when administered OD (once a day) 50mg ONGENTYS at every night bedtime(qhs) as compared to intake alone. [19]
- **Adverse effects:-** Most common adverse effect is Dyskinesia(involuntary movement) and other ADRs are given below in table. [20]

S.N.	ADRs	Placebo	ONGENTYS 25(mg)	ONGENTYS 50(mg)
1	Dyskinesia	6.2%	16%	20.4%
2	Constipation	1.9%	4.9%	6.4%
3	Insomnia	1.6%	7%	3.4%
4	Dry mouth	1.2%	6.6%	3%
5	creatine phosphokinase(CPK) increase	1.9%	2.9%	4.9%
6	Dizziness	1.2%	4.1%	3.4%
7	Somnolence	1.9%	4.1%	1.9%
8	UTI	0.8%	1.6%	3.8%
9	Weight decrease	0	0.4%	3.8%
10	Hallucinations	0.4%	2.5%	1.1%

Table.4 common adverse effect

Contraindications:-

- ✓ ONGENTYS is contraindicated with the concomitant use of Non-selective MAO inhibitors because both agents inhibit the metabolism of catecholamines leading to elevated level of catechomines which induce the risk of arrhythmias, abnormal heart rate and blood pressure.
- ✓ ONGENTYS is contraindicated in case of paraganglioma, pheochromocytoma and other catecholamines secreting neoplasms.
- ✓ Avoid ONGENTYS in case of severe hepatic impairment.[19]

Antidote for Opicapone:-

There is no specific antidote for Opicapone in case of Overdose toxicity, we can remove it by gastric lavage or by inactivation through activated charcoal. [19]

Non-clinical Toxicology:-

- **Carcinogenesis:-** No evidence was found of carcinogenesis when studies are carried out on mice and rats. To mice highest dose was administered more than 70 times to the recommended dose in human(RHD) i.e. 50mg for 2 years. In rat highest dose is tested more than 24 times to the RHD for 2 years. [19]
- **Mutagenesis:-** Opicapone was found negative in both *in-vitro* and *in-vivo* assays for mutagenesis.[20]

- **Fertility impairment:-** No evidence of fertility impairment was found in both male and female rats. Plasma exposure(AUC) was about 40 times at highest dose that in humans at RHD. [19]

Indications for patient:-

- ✓ ONGENTYS capsule should be taken at bedtime and do not eat food before 1 hour and at least 1 hour after administration of ONGENTYS.
- ✓ Avoid all the concomitant use of medication which are contraindicated with ONGENTYS.
- ✓ Inform to patient that after administration of ONGENTYS you may fall asleep hence intake it at bedtime.
- ✓ ONGENTYS may cause hypotension in PD patients.
- ✓ Dyskinesia is the major side-effect.
- ✓ Withdrawal of ONGENTYS may cause fever, muscle stiffness and confusion.
- ✓ ONGENTYS may induce gamble urges, sexual urges, urges to spend money, binge eating and other intensive urges due to increase in dopaminergic tone in the brain.
- ✓ If ONGENTYS dose is missed then take it on next scheduled time on next day. [19]

Conclusions:-

PD is a progressively growing neuro-degenerative disorder, which worsen as the time passes, various symptomatic treatments are available but the treatment which can stop the progression of PD is still required. Levodopa is a gold standard therapy for relieving symptoms of PD but the delivery of levodopa to the CNS is not an easy task, so many barriers are there to inhibit the proper transportation of levodopa from periphery to the CNS *(see flow diagram.1)* . Long exposure of levodopa is associated with the OFF-episodes phenomenon that creates serious problems in PD symptoms. During OFF-episode state Levodopa's effectiveness diminish between the dose regimen and symptoms are appeared before the time of next dose of levodopa. So many adjunctive medications are developed for tackling this issue but all these medications are associated with serious side-effects, In this row a new approach is developed i.e. ONGENTYS®(Opicapone). Opicapone is the third generation COMT inhibitor that inhibits the activity of COMT enzyme *(see the mechanism of action).* ONGENTYS® is the good approach to manage the OFF-episodes and possess less side-effects as compare to other COMT inhibitors introduced earlier. But there is still need of deep study on Opicapone safety and efficacy because the major side-effect of opicapone is Dyskinesia, Since dyskinesia is also associated with levodopa then adjunctive use of ONGENTYS® and Levodopa may synergistically develop dyskinesia in the PD patient. ONGENTYS® inhibits the metabolism of levodopa only in periphery but there is chance of metabolism of levodopa in CNS also by the COMT in this case we need to take another medications which inhibits metabolism of levodopa in CNS region like-Tolcapone, so there is need of another derivative or dosage form of opicapone that can work in both periphery as well as in CNS region by which we can avoid unnecessary use of other medications.

Abbreviation

SN.	Abbreviation	Description
1.	PD	Parkinson's Disease
2.	CNS	Central Nervous System
3.	COMT	Catechol-O-methyltransferase
4.	MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
5.	MPP+	1-methyl-4-phenylpyridinium
6.	GIT	Gastro Intestinal Tract
7.	MRI	Magnetic Resonance Imaging
8.	OCT	Optical Coherence Tomography
9.	DAT-SPECT	Dopamine transporter single-photon emission Computed tomography
10.	F-DOPA PET	Flourodopa positron Emission tomography
11.	DJ-1	Parkinson's disease protein 7

12.	GFAP	Glial fibrillary acidic protein
13.	BDNF	Brain-Derived Neurotrophic Factor
14.	BBB	Blood Brain Barrier
15.	AADC	Aromatic L-amino acid decarboxylase
16.	MAO	Monoamine oxidase
17.	DOPAC	3,4-Dihydroxyphenylacetic acid
18.	3-O-MD	3-O-methyldopa
19.	3-MT	3-methoxytayramine
20.	ADRs	Adverse Drug Reactions
21.	OD	Once a day
22.	TD	Thrice a day
23.	MDU	To be used as directed by physician
24.	mg	Milligram
25.	ON	Every Night
26.	BD	Twice a day
27.	OM	Every Morning
28.	L-dopa	Levodopa
29.	Isn't	Is not
30.	DBS	Deep Brain Stimulation
31.	T_{max}	Time at which drug plasma concentration is maximum
32.	C_{max}	Maximum drug plasma concentration
33.	AUC	Area Under the Curve
34.	RHD	Recommended Human Dose
35.	i.e	That is

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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