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L-DOPA COMPLICATIONS AND ENZYMATIC INHIBITORS IN PARKINSON DISEASE

Background information:

Parkinson disease was clinically described in 1817 by James Parkinson. This disease is considered as a neurodegenerative disorder that affects the extrapiramidal system, producing neuronal death and degeneration of different areas of the brain, including the substantia Nigra. The nerve cells of the substantia Nigra are in charge of producing dopamine, a fundamental neurotransmitter associated with movement. During the Parkinson disease we find two essential lesions: 1.) lack of dopamine in the substantia Nigra (that explains the motor symptoms) and 2.) Eosinophilic intracytoplasmatic fragments in neurons that are called Lewy Bodies. Although, the dopamine pathways are not the only affected, but also the serotoninergic and adrenergic pathways are altered, explaining different symptoms as none motor symptoms'.

So that we can understand this disease we must review the physiopathology of the basal nuclei's. The primary nuclei of the extrapiramidal system is the striatum, composed by the caudate and putamen, that receives impulses from the cortex of the brain by excitatory glutamate projections and from the compact portion of the substantia Nigra (Dopamine). The striatum projects impulses towards the reticular portion of the substantia Nigra and globus pallidus by GABAergic inhibitory impulses were as these two nuclei's

are the output unit of nerve impulses, from the basal ganglia towards the thalamus by projecting GABAergic inhibition. Then the thalamus projects excitatory glutamate impulses towards the medial premotor cortex, whose final result is to promote cortical arousal, activating agonist's muscles and facilitating voluntary movement. The indirect circuit of the basal nuclei's in addition has impulses from the striatum towards the external globus pallidus by GABAergic inhibition, then towards the subthalamic nuclei and finally towards the internal globus pallidus by excitatory glutamate impulses, giving has a final result the inhibition of the cortical activity and the antagonist muscles of the movement produced. It's important to remind that dopamine excites the direct pathway and inhibits the indirect pathway, promoting the cortical arousal. This means that Parkinson disease has a lack of dopaminergic impulses from the striatum and a hyperactivity of the subthalamic nuclei.

Parkinson disease characterizes by four cardinal motor symptoms and none motor symptoms. The most essential motor symptoms are: akinesia, resting tremor, stiffness and postural instability. Akinesia is the difficulty to initiate any movement in absence of paralysis; it's associated with bradikinesia (refers to a slow action movement, ex: Difficulty to initiate a movement or to sudden cease of any movement) and hipokinesia (refers to a decrease in the total of movements). Stiffness refers to tense muscles due to an increase of muscle tone, provoking reduction in the amplitude of the movements, pain and cramping in lower limbs, and diminishing facial expression. Postural instability refers to a stooped posture with a bending forward movement that contributes to disequilibrium, increasing the chance to have any type of accident. And last but not least, resting tremor, that refers to an involuntary movement during rest; in Parkinson this symptom begins in the limbs and

gradually disseminates to other parts of the body. The non motor symptoms are going to be explained later on in this review.

Also it's important to remind the reader about the **Dopaminergic System**. It is known that the Dopaminergic system denominated neuronal groups from A8 to A17 according to Fuxe's Classification. This neurons and its projections are grouped in three systems: Ultra Short system, formed by Dopaminergic cells located in the olfactory bulb (A16) and interplexiform neurons located in the retina (A17); Medium length system, formed by the tuberohipofisiario system, which originates Dopaminergic cells located in the hypothalamic arcuate nucleus and periventricular system, concluding there axons in the pituitary gland; neurons located in the dorsal and posterior hypothalamus (A13 y A14) which projections conclude in the anterior portion of the hypothalamus and septal lateral nuclei's. The last system implied is called Large system, formed by neurons located in retrorubral region (A8), the ventral tegmental area (A10) and the compact portion of the substantia nigra, giving projections towards the caudate and putamen nuclei's, limbic cortex and other nearby limbic structures such as (Cingulo).

Introduction:

Parkinson disease is a chronic and progressive neurodegenerative disorder that's considered as the second more often disease. It's more often in men than in women. The average age of Parkinson disease is around the sixth decade. It's considered that this disease is a heterogenic disorder were different variables affects the incidence that conduces towards this pathology, although it's a disease that doesn't conduces to death.

Now day's medical therapies are used to help patients that suffer this disorder to improve its quality of life to a similar normal way of life. Since the discovery of L-Dopa, principal drug used to treat this disorder; patients that suffered Parkinson disease were capable to reduce symptoms almost too normal. But the results weren't all as exceptional as we thought, these drug presented several problems that indicated investigators to add other drugs that helped L-dopa get into the brain. In this review were going to see which where the problems that caused the used of others drugs, to increase its effects and also the complications due to the prolonged use of L-dopa in patients with Parkinson disease.

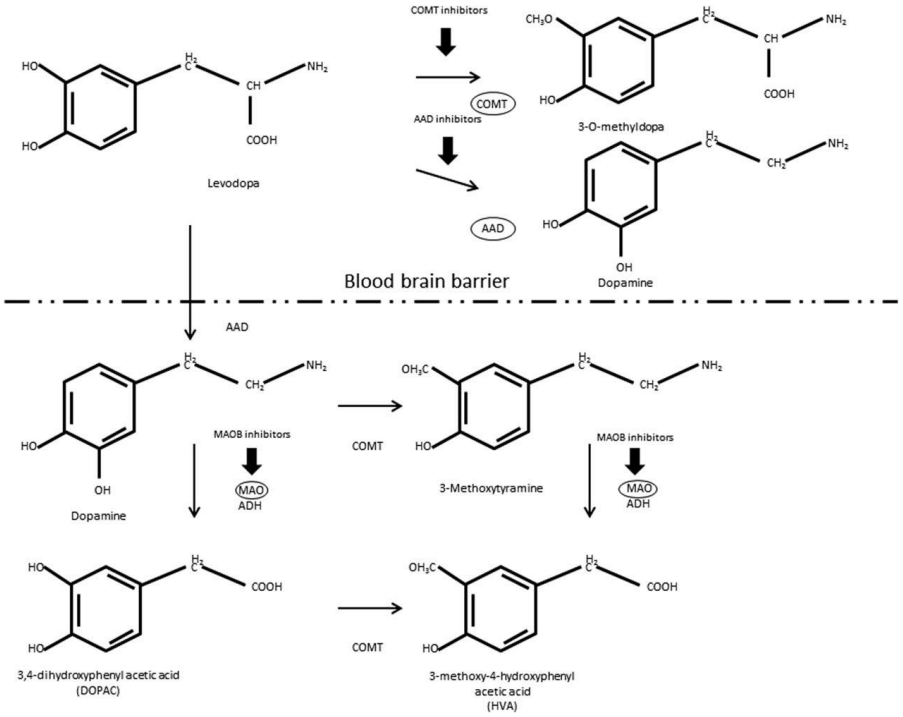
Pharmacokinetics of L-dopa:

L-dopa is the most efficient drug used in Parkinson disease. This drug is the precursor of dopamine which presented limitations when it was first used, such as: 1.) Dopamine does not pass the blood brain barrier (BBB), 2.) Present a decreased bioavailability because of the metabolic conversion of L-Dopa to dopamine at peripheral level and 3.) Frequent occurrence of adverse events. Other pharmacokinetics of importance: metabolized in the proximal portion of the small intestine and rapidly absorbed by an active transport of aromatics amino acids; Maximum plasmatic concentration will be between 0,5 to 2 hours after an oral doses administration; and its half life is from 1 to 3 hours.

Some limitations are important to emphasize such as the metabolic conversion of L-Dopa towards dopamine. This affects directly the bioavailability of the drug in the brain, because during peripheral level, some enzymes act directly over the L-dopa converting it into dopamine by decarboxilation, not allowing it to get to brain. These enzymes are: Dopa decarboxylase, central monoamine oxidase (MAO) and cathecol-O-methyl transferase

(COMT). Now we're going to comment briefly the functions of each enzyme and how does it affect L-dopa. The Dopa decarboxylase decarboxylates the L-Dopa to dopamine at peripherical level, decreasing the bioavailability of L-Dopa, producing small effects in the brain, meaning that this process needs to saturate so that a small amount of L-Dopa passes through the blood brain barrier, because dopamine doesn't pass the blood brain barrier. This is one of the most important limitations because it will need much bigger doses to produce the expected effects. Another enzyme such as the cathecol-O-methyl transferase (COMT) reduces the bioavailability because methylates L-Dopa into 3-O-Methyl Dopamine (3OMD), which competes with L-dopa to pass through the Blood brain barrier (BBB). COMT's are present mainly in the liver and in the brain, where a major proportion of L-dopa is metabolized to 3-O-Methyl Dopamine (3OMD). 3-O-Methyl Dopamine accumulates in the peripherical level and in the brain reaching its maximal level in blood concentration in one hour, meaning that it competes with L-dopa to pass through the BBB. Also it's important to know that 3-O-Methyl Dopamine has a half life of 15 hours approximately therefore explaining the significant accumulation and delayed clearance affecting the expected effects of the L-dopa and bioavailability. And the last enzyme, the monoamine oxidase (MAO), converts dopamine into 3,4-dihydroxiphenylacetic acid (DOPAC) and homovanillic acid (HVA). The mechanism in which dopamine is converted into this two substances mentioned above, is throughout two pathways after dopamine is released into the synaptic cleft by presynaptic dopaminergic neurons, recycling dopamine by the same dopaminergic neurons or by the degradation after the uptake by glial cells. During the reuptake of dopaminergic cells dopamine can follow two pathways: sequestration into the synaptic storage vesicles by monoamine transport system or present

an oxidative deamination by the monoamine oxidase converting it into 3,4-dihydroxiphenylacetic acid (DOPAC). The other pathway mentioned above by the glial cells uptake converts dopamine into homovanillic acid (HVA) with the help of COMT and MAO. Now we're going to continue to explain the different drugs that inhibit this types of enzymes and there efficiency with L-dopa.



Enzymatic inhibitors:

The peripheral decarboxylase inhibitors were drugs described by Bartholini in 1967, pointing out that this drugs where capable of blocking the activity of the enzyme (Dopa decarboxylase) in the periphery without crossing the blood-brain barrier (BBB). This resulted that in several combinations with L-dopa reduced the degradation of L-dopa into dopamine in the peripherical section, increasing as a consequence the amount of dopamine in the brain, the bioavailability of the drug without biotransformation, beneficial effects

such as an increment of L-dopa availability in de CNS, a prolonged half life of L-dopa; slow clearance rate of L-dopa in plasma and a decrease in 60 – 80% of the doses of L-Dopa in patients with Parkinson disease. Although this were effects found in the decarboxylase inhibitors, the enzyme Dopa decarboxylase presented other functions such as: 1.) participation in the conversion of L-5-hydroxitryptophan to serotonin and 2.) Catalytic metabolism of aromatic amino acids, meaning that its primary function of the enzyme was to provide essential neurotransmitters using pyridoxal phosphate as a cofactor and as a catalytic enzyme that decarboxylates aromatic amino acids, as mentioned above.

The drugs used in this group are:

Drug Name	Effects
Carbidopa	Inhibition of Dopa decarboxylase, used as a L-form, reducing doses in 22% of L-dopa in parkinsonian patients, plasma dopamine and homovanillic acid. Reduction of symptoms such as Nausea and vomit in 27% of patients, increasing tolerability in combined therapies. Although it was observed an increase in abnormal involuntary movements such as dyskinesia.
Benserazide	Reversible, peripheral Dopa decarboxylase inhibitor (DDCI) that doesn't pass the blood-brain barrier. In different studies this drug demonstrated a high tolerability with reduction symptoms such as nausea and vomit, but no difference in other side effects. Other parameters of interest where the safety of the drug pharmacokinetics, resulting in no significance influence. Compared towards Carbidopa, there were no different significance on dyskinesia, but a high frequency of nausea and vomit in L-dopa/Carbidopa.

The next group is the Monoamine oxidase inhibitors (MAOI). The monoamine oxidase (MAO) a mitochondrial enzyme that's involved as explained above in the oxidative deamination of several monoamines. This enzyme is present under two types of isoforms (MAOA and MAOB) that oxidase dopamine. The monoamine oxidase inhibitors that were

applied were non selective MAO and had results that limited the use by appearance of adverse events such as hypertensive crises associated to foods rich in tyramine (cheese and preserved foods) causing arterial hypertension through peripheral vasoactive mechanism limiting these drugs to a specific diet. These meant that non selective Monoamine oxidase inhibitors (MAOI) didn't work in the combinations with L-dopa. The development of specific Monoamine oxidase inhibitors (MAOI) was explored and successfully used because it inhibited the MAO-B and found out that these drugs intervene with neuroprotective effects.

The drugs used in this group are:

Drug Name	**Effects**
Selegiline	Irreversible inhibitor of MAO-B because forms a covalent bond with flavin adenine dinucleotide cofactor of MAO, meaning that the inhibitory MAO-B effect is longer than the drug elimination half life. Although it's considered a relative selective MAOBI because in higher doses the selectivity is lost. Other effects are: Inhibition of the uptake of catecholamines, inhibition of presynaptic catecholamine auto receptors, and release of catecholamine by amphetamine metabolites. Different studies have demonstrated that this drug doesn't reduce motor complications or dyskinesia. Although it reduces the doses of L-dopa.
Rasagiline	Selective, irreversible covalent bond MAO-B inhibitor that produces a metabolite called 1-aminoindan with no amphetamine-like activity. Doesn't have appreciable affinity to any catecholaminergic or serotoninergic receptor. Its selectivity is lost in higher doses. It's a neuroprotective and antiapoptotic drug. Some benefits of this drug combination were an increase in dopaminergic side effects such as nausea, orthostatic hypotension, increased dyskinesia, confusion and hallucination. Both drug combinations demonstrated a high tolerability and safety in patients treated.

And the last group of enzymatic inhibitors explained in this paper is the cathecol-O-methyl transferase inhibitors (COMTI). These drugs started to have importance on the treatment of Parkinson disease, because Dopa decarboxylase inhibitors shift the metabolism of the L-dopa towards the cathecol-O-methyl transferase (COMT) metabolic pathway. The first cathecol-O-methyl transferase inhibitor was introduced in 1958, with ineffective uses, unselective and high toxicity ranges. Over the 1980's second generation COMTI's were developed with specific properties for the inhibition of the enzyme. These new COMTI such as Tolcapone and Entacapone, determined that it inhibited the enzyme though other effects were also seen, such as an increase in the elimination half life of L-dopa up to an hour, a reduction of 3-O-methyldopamine (3OMD), an increase in 3,4-dihydroxiphenylacetic acid (DOPAC) and a decrease of homovanillic acid (HVA). These effects resulted in an increase of the duration of the effect of L-dopa and the increase of ON time, reducing OFF time as well.

The drugs used in this group are:

Drug Name	Effects
Tolcapone	Potent, selective and reversible nitrocatechol inhibitor of COMT that's acts in peripheral and centrally compartments. It has a high bioavailability. Its effects were showed on its efficacy in reducing the OFF effect in Parkinsonian patients with motor fluctuations, an increase in ON time effect (explained above) and reduction on doses of L-dopa when combined. Adverse effects showed an increase of preexisting dyskinesia and diarrhea, increase of liver enzymes, meaning that these patients must be monitored in liver function.
Entacapone	Selective and reversible nitrocatechol inhibitor of COMT that doesn't pass the BBB, meaning that it only acts at peripheral level.

	It shows an effective improvement in motor fluctuations by prolonging the effects of L-dopa. Also increases ON time and diminishes OFF time. Adverse events: Has no liver toxicity but it shoes dopaminergic effects such as vomit, nausea and dyskinesia and nondopaminergic effects such as diarrhea.

Complications of L-dopa treatment:

Motor fluctuations are the principal range L-Dopa induced complications. In general most studies are concentrated on motor fluctuations and L-Dopa Induced dyskinesia (LID). Risk factors implied in this type of complications include: disease progression (early and more severe, dyskinesia may occur in patients with more dopamine depletion), chronic L-Dopa therapy, altered sensitivity associated to compensatory processes, gene mutations (Polymorphisms and enzymatic mutations (DAT, OPRM1,DRD2,DRD3, HOMER 1 gene)) and individual doses of L-Dopa usage in early Parkinsonian patient. Though, certain types of patients with short exposure to L-Dopa are more likely to present this type of complications such as: tremor-dominant Parkinsonian patient, young-onset Parkinsonian patients, autosomal recessive Parkinsonian patients. Also it's important to remember that improvement in symptoms after L-Dopa administration is described as being "ON", whereas a return of parkinsonian symptoms is termed "OFF". The response to L-Dopa is divided into three time frames: beginning dose which switches on, peak dose which refers to a maximal improvement in symptoms and end of dose which symptoms return.

The most important motor fluctuations that readers must have in mind are: Predictable wearing off, Unpredictable or sudden-off, Dose failure and beginning of dose worsening and End of-dose rebound, and last ON-OFF fluctuations. Predictable wearing off becomes apparent when the duration of L-Dopa is 4 hours or less with intervals of doses are longer. Also this fluctuation becomes present usually during the morning before the first dose which is termed Morning akinesia. Unpredictable or sudden-off refers towards the return of parkinsonian symptoms unrelated to the timing of the medication; Often comes on over a few seconds resulting in severe, disabling akinesia. Dose failure and beginning of dose worsening and End of-dose rebound refers first towards a delayed clinical effect "Delayed ON", or even no effect termed "Dose failure". Dose Failure is associated towards slow gastric emptying in parkinsonian patients and presence of food, resulting in a reduced peripheral gastrointestinal absorption. During Beginning dose worsening some symptoms such as tremor are increased. In rare cases it shows exacerbations or rebound in symptoms at the end of dose. And last but not least, On-OFF fluctuations is the term to describe a predictable or unpredictable switching from being "ON" and mobile with dyskinesia to being "OFF" and immobile during the course of a day.

Other motor fluctuations to have in mind are related on the dependence of the dose of L-Dopa associated to Dyskinesia. Three clinical issues useful for managing dyskinesia are: Observation of movement phenomenology, to help distinguish the type of dyskinesia; Timing of dyskinesia in relation to the level of L-dopa; whether the patient is aware of the phenomenology. This is important because treating every dyskinesia is not necessarily essential. During high-dose dyskinesia it's common to find this phenomenology during the peak level of L-Dopa. It can be mixture of chorea, ballism, dystonia and myoclonus.

Symptom	Definition
Chorea	It's described as an involuntary, unpredictable body movement that do not have pattern. Its commonly form of peak-dose dyskinesia in limbs.
Ballism	It's described as an abnormal swinging jerking movement sometimes seen in chorea.
Dystonia	It's described as an involuntary and uncontrollable repetitive or twisting movement.
Myoclonus	It's described as a spontaneous, action induced or stimulus, sensitive or multifocal movement. It usually occurs within the first 10 -20 minutes of L-Dopa Dose
Ocular Dyskinesia	It's described as an involuntary eye movement that accompanies dyskinesia in other body parts. It´s shown has a slow and smooth reversal movement with a "to-and-fro" pattern.
Respiratory Dyskinesia	It's described as secondary symptom that affects respiratory muscles. It causes tachypnea, irregular rate and depth of breathing.

During Low-Dose Dyskinesia it can be find other symptoms such as: Off period Dystonia and Dysphasic Dyskinesia. Off period Dystonia occurs during off period and wearing off period tending to affect legs and feet. It's often seen during morning. Other rarer presentations are: Blepharospasm, jaw opening, neck posturing, hand dystonia and stridor. Dysphasic Dyskinesia occurs during the beginning or end dose referring towards the level of L-Dopa, rising or falling. It tends to affect the legs involving slow stereotypical alternating leg movement or unusual ballistic kicking.

Non motor fluctuations are another type of complication that needs to be evaluated in patients with Parkinson disease, because they are associated with L-Dopa administration and Dopamine agonists. The non motor fluctuations that were reported in several studies are: personality changes, hipersexuality, mood elevation confusion, hallucinations and psychotic episode, demonstrating a high impact on their quality of life, than motor features.

The neuropsychiatric aspects of the non motor fluctuations are classified in sensory, autonomic and neuropsychiatric fluctuations (seen in Table 2. “Adapted and modified from Riley and Lang,7 Fox and Lang,8 and Bayulkem and Lopez.9”). These classification reports symptoms such as: depressed mood, apathy, fatigue, anxiety, panic attacks and irritability (often in OFF state); euphoria, hyperactivity and hypomania are associated often with ON state. The frequency of these symptoms varies on the population, establishing the most frequently anxiety (66%), drenching sweats (64%), and slowness of thinking (58%), fatigue (56%), akathisia (54%), and irritability (52%). Although it’s important to remind, that these symptoms rarely come alone, most of the Parkinson Disease (PD) patients experienced more than one type of non motor fluctuation; also it’s important to remind professionals to have knowledge of the risk factors, because many of them overlap with risk factors of motor fluctuations. Some of the risk factors associated with PD are: younger age, depression, cognitive impairment, dementia and drug induced psychosis.

TABLE 2. Non-motor fluctuations

Sensory	Autonomic	Neuropsychiatric
Pain	Thermoregulation	Mood
Akathisia	Pallor	Anxiety, panic attacks
Paresthesias, sensory loss	Sweating, flushing	Depression
Restless legs syndrome	Skin temperature changes	Irritability, hypomania
Internal tremor	Sphincter function	Apathy
Sensory dyspnea	Urinary frequency	Fatigue
	Bloating, abdominal discomfort	Moaning, screaming
	Constipation	Psychotic
	Cardiovascular function	Euphoria, agitation
	Blood pressure changes	Hypomania, mania
	Tachycardia	Hallucinations
	Dysphagia, drooling, dry mouth	Delusions
	Pupillary dilation?	Cognitive changes
	Dyspnea, laryngeal stridor	Sexual function
	Peripheral edema	Hypersexuality
		Aberrant sexual behavior

The fluctuation of non motor symptoms according to the on and off state suggest an involvement of dopaminergic systems in the pathophysiology of Non motor fluctuations. Some studies made with L-Dopa monotherapy demonstrated that mood changes were independent of psychological impact in Parkinson disease meaning that there were different symptoms that showed benefits towards these patients, such as decreased anxiety and elevation in mood. Other studies showed physiologically an increased cerebral blood flow in the posterior cingulate cortex in mood fluctuations in patients with anxiety and depression, meaning that the dopaminergic system influenced independently from its projections, the emotional regulation.

Punding is another of the non motor fluctuations symptoms characterized by an "*intense fascination with excessive, repetitive, non-goal-orientated behaviors, such as repetitive manipulations of technical equipment, continual handling, examining, and sorting of common objects, grooming, hoarding, pointless driving or walkabouts, and the engagement in extended monologues devoid of content.*" Other characteristics of this symptom are: sex, premorbid occupations or hobbies and diminished of their own quality of life such as in sleep deprivation and decrease in the ingestion of food, taking disruptive attitudes associated with obsession and compulsions. There have been different theories to explain this symptom in patients with Parkinson disease, such as the habit of learning. This theory stipulates an overstimulation over the ventral striatum inducing therefore a transition from goal learning to habit learning, because of a lack of dopaminergic cell projections to the dorsal striatum in PD patients and a relative preservation of these projections towards the ventral striatum.

Another drug induced behavioral change in Parkinson Disease (PD) patients are part of the **Dopamine dysregulation syndrome (DDS)**. This syndrome refers to an "*addictive pattern of medication usage, characterized by the intake of large doses of dopaminergic drugs in excess of the required to control the motor fluctuations*". The DDS is frequently associated with dyskinesia, hypomania, mania and psychosis in short potent drugs such as L-Dopa. Risk Factors for DDS include: young age in PD patients, high alcohol intakes and depression. Other factors are taken as high evidence towards this syndrome such as familiar history of PD. Its pathophysiology it's determined by the theory of addiction, stipulating that the drug has different effects such as euphoria. Other theories of implied chronic use of drugs are associated with the habit theory (the intake of the drugs becomes an autonomic

learned behavior), Hedonic homeostatic dysregulation theory (the usage of drugs are implied to diminish negative response of symptoms in DDS) and salience theory (Chronic drug usage modifies the sensibility of receptors, increasing dopamine release in the ventral striatum in response of L-Dopa).

Psychosis is another non motor fluctuation, considered as a symptom in Parkinson disease. It's associated with **hallucinations** that are frequent in PD patients, characterized by complex, and well formed ideas, consisting in children or animals. It's often that visual hallucinations (60 – 85%) are found in this type of patients, and they may or may not be accompanied by delusions. They tend to occur frequently during dim light or in dark, although they might occur during the day. Unlike, schizophrenia, visual hallucinations in patients with PD is not associated with emotional content. Other types of visual hallucinations are recalled to pass under recognized such as diplopia, illusions, passage hallucinations and presence hallucinations. Delusions are often associated with jealousy (Othello Syndrome), to paranoia delusions, delusional misidentification syndrome, Capgras Syndrome, Fregoli Syndrome and reduplicative paramnesia. Its physiopathology is unknown because of lack of investigations, therefore separating disease-related and medication usage in psychosis is difficult. Although it exists a theory that determines an association with hypersensitivity of limbic DA receptors, that predisposes to psychosis.

Hypomania and mania are other symptoms that are associated with PD patients with L-Dopa treatment or occur with DDS. It's infrequent to find these symptoms with PD patients. Although professionals mustn't discard this when associated with other non motor

fluctuations such as dyskinesia, ICDs, DDS, and psychosis or in dopamine replace treatment (DRT).

Last, professionals must have in mind another type of non motor fluctuation called **impulse control disease (ICD)**. This non motor fluctuation refers "*as a failure to resist an impulse, drive, or temptation to perform an action despite negative consequences*". The most frequent ICDs reported in PD patients are: pathological gambling, hipersexuality, compulsive shopping, and compulsive eating. This type of non motor fluctuation can be associated with other type of compulsive abnormal behavior such as DDS and punding. The most frequent ICD reported with Dopamine agonists (DA) use where, hyper sexuality and aberrant sexual behaviors. Also hyper sexuality induced by L-dopa can occur in context of hypomania and mania. It's important to remind that studies have shown a high prevalence of ICD in patients treated with DAs compared with those not taking DA. Risk factors associated with ICD reported in several studies were: young age, personal or family history of alcohol abuse, caffeine and cigarettes, gambling problems, motor complications, and high novelty seeking or impulsivity personality. ICDs physiopathology described in several studies with induced DA and L-Dopa

Conclusions:

It's important to remind that the use of enzymatic inhibitors has proved beneficial effects towards Parkinson treatment increasing tolerability and safety on certain pharmacokinetics parameters. Although some of the enzymatic inhibitors increase some adverse events, it potentiates the L-dopa effect and duration of its action, meaning that this

drug combined with enzymatic inhibitors will stay as a main treatment for Parkinson disease.

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