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BROMOCRIPTIN AND PERGOLIDE TREATMENT ON PARKINSON DISEASE

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A. PARKINSON DISEASE DEFINITION

Parkinson disease (PD) was first described by dr. James Parkinson in 1817 as "shaking palsy" (DeMaagd and Philip, 2015). PD is a disease with a degenerative process involving dopaminergic neurons in substantia nigra (the area of basal ganglia which produces and stores dopamine neurotransmitter). This area is important in extrapyramidal system which controls posture and coordination of body movements (Wagner, 2008). Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease (Rizek, Kumar and Jog, 2016; Elbaz, 2016).

B. EPIDEMIOLOGY AND ETIOLOGY

Parkinson's Disease (PD) is one of paralysis disease in United States. This disease occurs in one out of one hundred patients with age over 60 years and occurs more in men than women, and is quite rare in patients with age under 40 years. Parkinson's disease attacks population from various ethnic and socioeconomic background (Wagner, 2008).

The etiology of Parkinson's disease is still unknown, or idiopathic. However, genetic factor, environmental factor, or a combination of both might illustrate why nerve cells in substantia nigra are deteriorating. In addition, another possible causes of Parkinson's disease are abnormal reaction to virus, exposure to toxic substances, and premature or accelerated aging (Wagner, 2008).

Parkinson's disease is caused by brain cells damage, especially in substantia nigra, which has an important function in production and storage of dopamine. When a patient is diagnosed with Parkinson's disease, the patient loses 50-60% of dopamine neurons in substantia nigra

and the rest of existing neurons do not function properly, as a result the patient cannot control/withhold voluntary movements. Cell death pathogenesis (neuronal degeneration) occurs due to oxidative stress, mitochondrial dysfunction, increased excitotoxic concentration of amino acids and inflammatory cytokines, immune system disorders, tropic factor deficiency, apoptotic signals, and environmental factors (Wagner, 2008).

Conditions that can cause oxidative stress are an increase in monoamine oxidase B metabolism or a decrease in glutathione clearance from free radicals that can cause dysfunction and cell death. Environmental toxins that are suspected to cause Parkinson's disease include 1-methyl-4-phenyl-1-2-5-6-tetrahydropyridine (MPTP), carbon monoxide, manganese, methanol, hydrogen sulfide, petrochemicals and pesticides. In addition, the use of drugs that can reduce dopamine center and worsen Parkinson's symptoms include several antipsychotics, amoxapine, anti-nausea (prochlorpromazine and metoclopramide) (Wagner, 2008).

C. PATOPHYSIOLOGY

In general, Parkinson's disease occurs due to a decrease of dopamine levels following neuron cell death in substantia nigra that occurs up to 50-60% neuron cells. Substantia nigra (often called as black substance) is a small region of brain (brain stem) located just above the spinal cord. This section becomes the center of control / coordination of all movements. The cells produce a neurotransmitter called dopamine, which regulates all muscle movements and body balance that are controlled by central nervous system. Dopamine is needed as electrochemical communication between neuronal cells in brain, especially in regulating movements, postural balance and reflexes, and communication fluency (speech) (Wagner, 2008).

Substantia nigra sends nerve fibers to corpus striatum, which is a part of basal ganglion in brain. Corpus striatum consists of nucleus and lentiform nucleus consisting of pallidum (globus pallidus) and putamen. This reduction causes decrease of neuronal activity in corpus striatum and basal ganglion. In addition, these various chemicals are active in basal ganglia such as acetic acid, histamine, glutamate, serotonin, dopamine, norepinephrine, epinephrine, γ-aminobutyric acid (GABA), enkephalins, substance P, and adenosine. However, some of these neurotransmitters concentration are decreased in the brain as a result of degeneration from norepinephrine neurons in locus ceruleus and acetylcholine neurons in the basal nucleus, vagus, bone marrow and the autonomic peripheral system. This decrease in neurotransmitters can cause some symptoms of Parkinson's disease, such as loss of dopamine

and norepinephrine neurons in limbic system can cause depression and anxiety, and loss of neurons in hippocampus and amygdala from limbic system can cause cognitive damage. Another result is loss of neuronal circuit control in basal ganglion to regulate the movement type and cause all neuron functions in central nervous system (CNS) to decrease and produce slowness of movement (bradykinesia), tremors, rigidity and loss of postural reflexes (Wagner, 2008).

Anatomy of extrapyramidal system where it functions as a control system for muscle movement through a system of pathways and nerve channels that connects cerebral cortex, basal ganglia, thalamus, cerebellum, reticular formation, and spinal neurons can be seen in Figure 1 below:

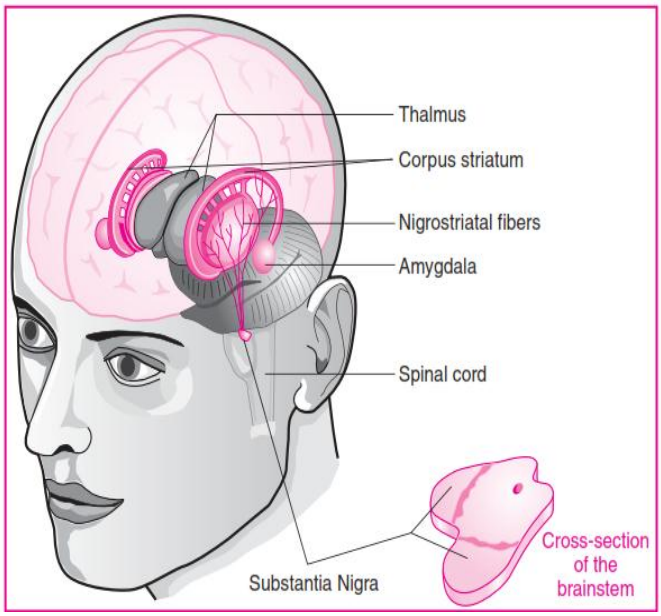


Figure 1: Extrapyramidal system anatomy (Wagner, 2008).

D. CLINICAL MANIFESTATION

Cardinal signs for Parkinson's Disease are as follows (Delong and Juncos, 2010; Wagner, 2008; Wells *et al*., 2009):

(1) Tremor

Eighty five percent patients will experience tremor. The tremor mainly occurs during resting time and mostly occurs in hand. Tremor increases if the patient is tired and experiences emotional tension.

(2) Stiffness (Rigidity)

Stiffness is always present in Parkinson's patients following increased muscle tone, both the flexor and extensor muscles will contract strongly. Stiffness appears on the face, making the face appears like a mask because of limited facial expression, eye blinking becomes less frequent, body posture becomes bent forwardly, arms and legs are in a state of mild flexion, and patient will take smaller steps during walking.

(3) Bradykinesia

Bradykinesia is characterized by abnormal slowness in voluntary movements. During bradykinesia these might follow:

- Postural damage, gait disturbance.
- Autonomic damage such as urinary incontinence, constipation, orthostatic hypotension, sweating, oily skin.
- Impaired vision, where vision becomes blurred because it is unable to maintain eye muscles contraction.
- Excessive fatigue and muscle ache due to stiffness.
- Impaired respiratory function such as hypoventilation and reduced airway clearance.
- Behavioral and mental disturbances, and the possibility of dementia and memory impairment, as well as depression.

(4) Postural instability

Postural instability often causes risk of falling in Parkinson’s patients.

E. DIAGNOSIS

Parkinson’s disease can be diagnosis if there are 2 out of these clinical signs that are present. The clinical signs are:

- Stiffness of skeletal muscle
- Resting tremor
- Bradykinesia
- Postural instability, and
- Positive response to anti Parkinson (Wells *et al*., 2009).

According to Wells *et al.* (2009), more detailed diagnosis of Parkinson's disease can be seen at Figure 2 as follows:

TABLE 55-1 Presentation of Parkinson's Disease (PD)

General features

For clinically probable PD, the patient exhibits at least two of the following: resting tremor, rigidity, or bradykinesia. Asymmetric onset (unilaterality) of these features is usual.

Postural instability (difficulty with maintaining balance) is more common in advanced PD.

Motor symptoms

The patient experiences decreased manual dexterity, difficulty arising from a seated position, diminished arm swing during ambulation, dysarthria (slurred speech), dysphagia (difficulty with swallowing), festinating gait (tendency to pass from a walking to a running pace), flexed posture (axial, upper/lower extremities), "freezing" at initiation of movement, hypomimia (reduced facial animation), hypophonia (reduced voice volume), and micrographia (diminution of handwritten letters/symbols).

Autonomic and sensory symptoms

The patient experiences bladder and anal sphincter disturbances, constipation, diaphoresis, fatigue, olfactory disturbance, orthostatic blood pressure changes, pain, paresthesia, paroxysmal vascular flushing, seborrhea, sexual dysfunction, and sialorrhea (drooling).

Mental status changes

The patient experiences anxiety, apathy, bradyphrenia (slowness of thought processes), confusional state, dementia, depression, hallucinosis/psychosis (typically drug-induced), and sleep disorders (excessive daytime sleepiness, insomnia, obstructive sleep apnea, and rapid eye movement sleep behavior disorder).

Laboratory tests

No laboratory tests are available to diagnose PD.

Other diagnostic tests

Genetic testing is not routinely helpful.

Neuroimaging may be useful for excluding other causes of PD.

Medication history should be obtained to rule out drug-induced parkinsonism

Figure 2: Diagnosis of Parkinson's Disease (Wells *et al.*, 2009).

According to Delong and Juncos (2010), differential diagnosis of Parkinson's disease can be seen at Figure 3 and Figure 4 as follows:

DIFFERENTIAL DIAGNOSIS OF PARKINSONISM

Primary Parkinsonism

- Genetically based PD (see Table 24-1)
- Idiopathic ("sporadic") PD (most common form)
  - Phenotype may be influenced by "vulnerability" genes and environmental factors
- Other neurodegenerative disorders
  - Disorders associated with α-synuclein pathology
    - Multiple system atrophies (glial and neuronal inclusions)
      - Striatonigral degeneration
      - Olivopontocerebellar atrophy
      - Shy-Drager syndrome
      - Motor neuron disease with PD features
    - Dementia with Lewy bodies (cortical and brainstem neuronal inclusions)
  - Disorders associated with primary tau pathology ("tauopathies")
    - Progressive supranuclear palsy
    - Corticobasal degeneration
    - Frontotemporal dementia
  - Disorders associated with primary amyloid pathology ("amyloidopathies")
    - Alzheimer's disease with parkinsonism
- Genetically mediated disorders with occasional parkinsonian features
  - Wilson's disease
  - Hallervorden-Spatz disease
  - Chédiak-Hagashi syndrome
  - SCA-3 spinocerebellar ataxia
  - X-linked dystonia-parkinsonism (DYT3)
  - Fragile X premutation associated ataxia-tremor-parkinsonism syndrome
  - Huntington's disease (Westphalt variant)
  - Prion disease
- Miscellaneous acquired conditions
  - Vascular parkinsonism
  - Normal pressure hydrocephalus
  - Catatonia
  - Cerebral palsy

Figure 3: Differential Diagnosis of Primary Parkinsonism (Delong and Juncos, 2010).

Secondary Parkinsonism
Repeated head trauma ("Dementia pugilistica" with parkinsonian features)
Infectious and postinfectious diseases
Postencephalitic PD
Neurosyphillis
Metabolic conditions
Hypoparathyroidism or pseudohypoparathyroidism with basal ganglia calcifications
Non-Wilsonian hepatolenticular degeneration
Drugs
Neuroleptics (typical antipsychotics)
Selected atypical antipsychotics (see text)
Antiemetics (e.g., compazine, metoclopramide)
Dopamine-depleting agents (reserpine, tetrabenazine)
α-Methyldopa
Lithium carbonate
Valproic acid
Fluoxetine
Toxins
1-Methyl-1,2,4,6 tetrahydropyridine (MPTP)
Manganese
Cyanide
Methanol
Carbon monoxide
Carbon disulfide
Hexane

Figure 4: Differential Diagnosis of Secondary Parkinsonism (Delong and Juncos, 2010).

F. TREATMENT OF PARKINSON'S DISEASE

The principles of Parkinson's Disease treatment are lifestyle changes, adequate nutrition and exercise, pharmacological treatment, especially by using drugs that can increase dopamine concentration, and surgical therapy if the patient fails to respond to pharmacological intervention. The goal of treatment is to maintain the condition of patient so the patient manages to do their daily activities and maintain quality of life by reducing patient symptoms, minimizing the development of fluctuating responses and limiting the use of drugs that can have adverse effects on patients (Wagner, 2008; Wells et al., 2009).

Treatment of Parkinson's disease can be grouped into these following classes (Wagner, 2008; Wells et al., 2009):

(1) Pharmacological treatment

Pharmacological treatment includes drugs that have mechanism of action in:

- Dopaminergic system, include:

1. Dopamine replacement drug

Include levodopa, which is the first-line drug for Parkinson's disease. In brain, especially in dopaminergic neurons by L-aromatic amino acid decarboxylase, levodopa is converted to dopamine. Levodopa will reduce tremor, muscle stiffness and might improve body movement. Patients with mild Parkinson's disease can resume their normal activities. This drug is given with carbidopa to increase its efficacy and reduce its side effects.

2. Dopamine agonist

This class of drug will work by stimulating dopamine receptors, but it can also cause a progressive decrease in dopamine receptor which in turn leads to an increase in Parkinson's symptoms. This class of drug is also useful for patients who have experienced fluctuating attacks and dyskinesias as a result of high doses of levodopa.

3. Monoamine oxidase inhibitor (MAO Inhibitor)

This class of drug is useful for Parkinson's disease because dopamine neurotransmission can be increased by preventing its destruction. This class of drug will reduce Parkinson's symptoms by inhibiting monoamine oxidase B (MAO-B), thereby inhibiting the destruction of dopamine released by dopaminergic neurons and improve body movements.

- **Cholinergic system, include**

1. Anticholinergic drug

This drug inhibits cholinergic system in basal ganglia and inhibits brain neurotransmitters actions. This drug balances dopamine and acetylcholine, thereby reducing tremor symptom.

- **Glutamatergic system, include**

1. Amantadin

This drug acts as a substitute for dopamine, but works in other parts of brain. This drug reduces tremor symptom, bradykinesia and fatigue in early Parkinson's disease and can eliminate motoric fluctuations and dyskinesias in patients with advanced Parkinson's disease. This drug can be used as a monotherapy or as a combination with levodopa or dopamine agonists.

(2) Non-pharmacological treatment

Non-pharmacological treatment of Parkinson’s disease are as follows:

- Education to patients their family
- Rehabilitative treatment and life style changes
- Exercise
- Adequate nutritional intake

(3) Surgical treatment

Surgical treatment is indicated if the patient fails to respond to pharmacological treatment. Surgical treatments of Parkinson’s disease are as follows:

- Pallidotomy or thalamotomy
- Deep-Brain Stimulation (DBS)
- Transplantation

Figure 5 below shows Parkinson's disease treatment management algorithm:

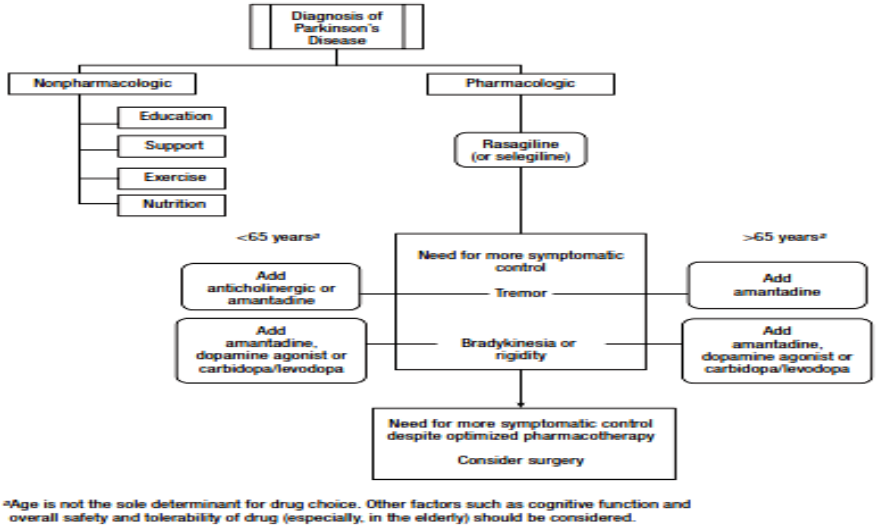


Figure 5: Parkinson's Disease Treatment Management (Wells *et al.*, 2009).

Pharmacological treatment that can be given to Parkinson's disease patients can be seen at Figure 6 and Figure 7 as follows:

Generic Name (Trade Name)	Mechanism of Action and Receptor Specificity	Dosing
Levodopa (Larodopa®, Dopar®) Carbidopa (Lodosyn®)	LD metabolized to DA CD blocks peripheral conversion of LD to DA and increases LD CNS penetration	Start with Sinemet® ½ tab (100 mg LD, 25 mg CD) twice daily for 1 week, then ½ tab three times daily; then, increase by ½ tab daily every week; usual MD is 300–2000 mg daily; since the duration of LD is 2 to 3 hours, patients may require doses every 2 hours
Levodopa/Carbidopa (Sinemet®) (Parcopa™ with phenylalanine) (Sinemet CR®)	Standard, immediate-release LD Rapid-dissolving LD Controlled-release LD	Sinemet CR: Start with 1 tab (100 mg LD, 25 mg CD) two or three times daily; as symptoms increase, use 200 mg LD tab 2–4 times daily; usual MD is 200–2200 mg daily
Apomorphine (Apokyn®)	Activate postsynaptic D1 and D2 DA receptors	Start an antiemetic for 3 days, then give apomorphine 2 mg SC injection (1 mg if outpatient) while monitoring blood pressure; then increase by 1 to 2 mg every 2 or more hours; usual MD is 2–6 mg 3–5 times daily for off periods
Pergolide (Permax®)	Activate postsynaptic D1 and D2 DA receptors	Start with 0.05 mg daily and increase by 0.05–0.15 mg daily every few days over several weeks to a usual MD of 0.5–1 mg three times daily (maximum 5 mg daily)
Bromocriptine (Parlodel®)	Activate postsynaptic D2 and blocks D1 DA receptors	Start with 1.25 mg daily at bedtime, then 1.25 mg twice daily; on week 2, increase to 2.5 mg twice daily, then increase by 2.5 mg daily every 2–4 weeks up to 15–45 mg daily divided 2–3 times daily
Pramipexole (Mirapex®)	Activate postsynaptic D2 DA receptors	Start with 0.125 mg three times daily; increase about weekly by 0.375–0.75 mg/day to a MD of 0.5–1.5 mg three times daily; dosage reduction needed in patients with creatinine clearance less than 60 mL/minute
Ropinirole (Requip®)	Activate postsynaptic D2 DA receptors	Start with 0.25 mg three times daily; increase about weekly by 0.75–1.5 mg daily to a MD dose of 3–8 mg three times daily
Selegiline (Eldepryl®)	Blocks MAO_B metabolism and presynaptic reuptake of DA in the brain	Start with 5 mg in the morning; if symptoms continue, add 5 mg at noon; 5 mg daily may be as clinically effective as 10 mg daily with fewer side effects
(Zelapar® with phenylalanine)	Rapid-dissolving selegiline	Start with 1.25 mg every morning before breakfast; if symptoms continue after 6 weeks, increase dose to 2.5 mg every morning. Avoid food or liquid for 5 minutes before or after the dose
Rasagaline (Azilect®)	Blocks MAO_B metabolism	Start with 0.5 mg daily if symptoms continue, increase to 1 mg daily
Tolcapone (Tasmar®)	Peripherally blocks COMT metabolism of DA; some central activity	Start with 100 mg with first Sinemet® dose once daily; if symptoms continue, increase to 2 and then 3 times daily, then to 200 mg each dose; usual MD is 100 three times daily to minimize risk of side-effects
Entacapone (Comtan®)	Peripherally blocks COMT metabolism of DA	Take a 200-mg tab with each Sinemet® dose up to 8 tabs daily; usual MD is 200 mg 3–4 times daily; decrease dose by 50% with hepatic impairment
CD/LD/Entacapone (Stalevo®)	See CD, LD, and entacapone	Usual MD is 300–1200 mg LD daily; the largest strength tab contains 150 mg LD and 200 mg entacapone; patients requiring larger LD doses will need additional LD medication; titrate as with LD
Amantadine (Symmetrel®)	NMDA-receptor antagonist that blocks glutamate transmission, promotes DA release, and blocks Ach	Start with 100 mg daily at breakfast; after 1 week, add 100 mg daily in the early afternoon; decrease dose as creatinine clearance decreases less than
Anticholinergics (various, including trihexyphenidyl, benztropine)	Block Ach, decrease Ach: DA ratio	80 mL/minute

Ach, acetylcholine; CNS, central nervous system; CD, carbidopa; COMT, catechol-O-methyltransferase; D1, a class of dopamine receptors which includes D_1 and D_5 subtypes; D2, a class of dopamine receptors which includes D_2, D_3, and D_4 subtypes; DA, dopamine; LD, levodopa; MAO, monoamine oxidase; MD, maintenance dose; NMDA, N-methyl-D-aspartate.

Figure 6: Pharmacological Treatment of Parkinson's Disease (Wagner, 2009).

LEVODOPA FORMULATIONS AND DOPAMINE AGONISTS USED IN PARKINSON'S DISEASE

AGENTS	LD DOSE EQUIVALENCY	AVAILABLE STRENGTHS (MG)	INITIAL DOSING	COMMENTS
Carbidopa/Levodopa (Typical Initial Strength)				
Carbidopa/levodopa IR 25/100	100 mg (levodopa anchor dose)	10/100 25/100 25/250	25/100; 0.5–1 tab tid	Usual range = 300–800 mg/d with typical schedules being q8h to q3h.
Carbidopa/levodopa CR 50/200	150 mg	25/100 50/200	50/200; 1 tab bid to tid	Increased bioavailability with food. Splitting the tablet negates the CR properties. Usual schedule is q8h to q4h.
Carbidopa/levodopa/ entacapone 25/100/200	120 mg	12.5/50/200 25/100/200 37.5/150/200	25/100/200; 1 tab bid to tid	Do not split tablets. May combine with Sinemet IR. Usual schedule is q8h to q4h.
Parcopa 25/100	100 mg	25/100 25/250	25/100; 1 tab tid	Can be used as regular or supplemental rescue doses in cases of regular dose failure. Orally dissolved without water.

Dopamine Agonists	Approximate Target Doses				
	DA EQUIVALENT TO ABOVE LD ANCHOR DOSE	AVAILABLE STRENGTHS (MG)	INITIAL DOSING	MONOTHERAPY	AS ADJUNCTS TO LD	OTHER CONSIDERATIONS
Non-ergot alkaloids						
Pramipexole	1 mg	0.125, 0.25, 1, 1.5	0.125 mg tid	1.5–4.5 mg/d	0.375–3.0 mg/d	Renal metabolism; dose adjustments needed in renal insufficiency. Occasionally associated with "sleep attacks."
Ropinirole	5 mg	0.25, 0.5, 1, 2, 3, 4, 5	0.25 mg tid	12–24 mg/d	6–16 mg/d	Hepatic metabolism; potential drug-drug interactions. Occasionally associated with "sleep attacks."
Ropinirole extended release	Availability pending.					
Rotigotine		2, 4, 6	2 mg/24 h	6 mg/d	2–6 mg/d	Available as transdermal patch.
Ergot alkaloids						
Bromocriptine	2 mg	2.5, 5.0	1.25 mg bid to tid	7.5–15 mg/d	3.75–7.5 mg/d	Rare reports of pulmonary and retroperitoneal fibrosis. Relative incidence of sleep attacks not well studied.
Pergolide	Removed from U.S. market in 2007. See text.					
Cabergoline	Used in select cases of PD in Europe. Not approved for the treatment of PD in the U.S.					

Note: Equivalency doses are approximations based on clinical experience, may not be accurate in individual patients, and are not intended to correlate with the in vitro binding affinities of these compounds.
DA, dopamine agonist; IR, immediate release; CR, controlled release; LD, levodopa (with carbidopa).
Carbidopa/levodopa/entacapone = Stalevo.

Figure 7: Pharmacological Treatment of Parkinson's Disease (Delong and Juncos, 2010).

According to Wells *et al.* (2009), drugs that can be used as Parkinson's disease treatment are as follows (Figure 8).

TABLE 55-2 Drugs Used in Parkinson's Disease

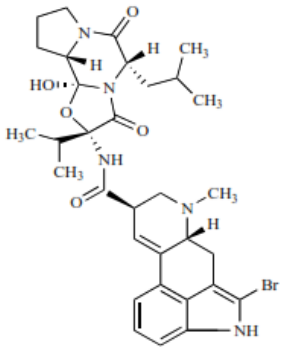
Generic Name	Trade Name	Dosage Range[a] (mg/day)	Dosage Forms (mg)
Anticholinergic drugs			
Benztropine	Cogentin	0.5–4	0.5, 1, 2
Trihexyphenidyl	Artane	1–6	2, 5
Carbidopa/levodopa products			
Carbidopa/L-dopa	Sinemet	300–1,000[b]	10/100, 25/100, 25/250
Carbidopa/L-dopa ODT	Parcopa	300–1,000[b]	10/100, 25/100, 25/250
Carbidopa/L-dopa CR	Sinemet CR	400–1,000[b]	25/100, 50/200
Carbidopa/L-dopa/entacapone	Stalevo	600–1,600[c]	12.5/50/200, 25/100/200, 37.5/150/200
Carbidopa	Lodosyn	25–75	25
Dopamine agonists			
Apomorphine	Apokyn	3–12	30 per 3 mL
Bromocriptine	Parlodel	15–40	2.5, 5
Pramipexole	Mirapex	1.5–4.5	0.125, 0.25, 0.5, 1, 1.5
Ropinirole	Requip	9–24	0.25, 0.5, 1, 2, 3, 4, 5
Rotigotine	Neupro	2–6	2, 4, 6
COMT inhibitors			
Entacapone	Comtan	200–1,600	200
Tolcapone	Tasmar	300–600	100, 200
MAO-B inhibitors			
Rasagiline	Azilect	0.5–1	0.5, 1
Selegiline	Eldepryl	5–10	5
Selegiline ODT	Zelapar	1.25–2.5	1.25, 2.5
Anticholinergic drugs			
Benztropine	Cogentin	0.5–4	0.5, 1, 2
Trihexyphenidyl	Artane	1–6	2, 5, 2/5 mL
Miscellaneous			
Amantadine	Symmetrel	200–300	100

COMT, catechol-O-methyltransferase; CR, controlled release; MAO, monoamine oxidase; ODT, orally disintegrating tablet.
[a]Dosages may vary beyond stated range.
[b]Dosages expressed as L-dopa component.
[c]Dosages expressed as entacapone component.

Figure 8: Pharmacological Treatment of Parkinson's Disease (Wells *et al.*, 2009).

G. BROMOCRIPTINE

Bromocriptine chemical structure can be seen below:



Bromocriptine

Figure 9. Bromocriptine Chemical Structure.

(Simola *et al*., 2010).

Bromocriptine is an ergot derivate drug that functions as a dopamine agonist in Parkinson's disease treatment. It activates dopamine receptors, postsynaptic D2 and blocks dopamine D1 receptors. Bromocriptine can be used as monotherapy for the management of Parkinson's syndrome early symptoms and to treat patients who have experienced fluctuating attacks and dyskinesia as a result of high doses of levodopa (Lacy et al., 2009; Wagner, 2008).

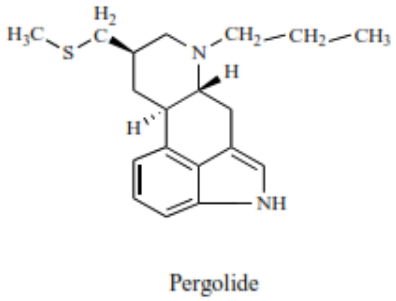
Bromocriptine dose used for Parkinson's disease treatment, which is given orally is 1.25 mg twice a day at night before bed, can be increased up to 2.5 mg / day for 2-4 weeks (the usual dosage range is 30-90 mg / day divided into 3 doses; maximum dose: 100 mg / day), for elderly patients (> 70 years) lower dose can be given. Bromocripitine pharmacokinetic is described as follows (Lacy et al., 2009; McEvoy et al., 2011; Sweetman, 2009; Wagner 2008):

- Onset of action : Prolactin decreasing effect : 1-2 hours
- Protein binfd : 90% to 96% (mainly to albumin)
- Metabolism : Primarily through hepatic metabolism via CYP3A; extensive first-pass biotransformation
- Bioavailability : 28%, with its peak plasma concentration at 1-3 hours.
- Half life (t ½) : 15 hours (8-20 hours)
- Peak serum time : 1-3 hours
- Excretion : Primarily through faeces and urine (2% - 6% as unchanged drug metabolite)

Nausea is the most common side effect that occurs at the beginning of treatment, this is caused by its stimulation that triggers chemoreceptor trigger zone (CTZ) in postrema area located outside the blood-brain barrier, to reduce nausea, bromocriptine can be taken together with food or domperidone 1 hour before bromocriptine consumption. Other side effects such as vomiting, dizziness and orthostatic hypotension, leg and retroperitoneal edema, pulmonary fibrosis, and hallucinations might also present. Another side effects that have been reported are headache, drowsiness, dry mouth, constipation, diarrhea, and altered liver function test results. Dyskinesia and psychomotor excitation also occur in Parkinson's disease, this is why bromocriptine might also progressively decrease dopamine receptors which will further increase and worsen Parkinson's symptoms, especially in patients who already have dyskinesia. Dyskinesia that occurs in early stages of Parkinson's treatment is usually of overtreatment, thereby dose reduction or drug fractionation is needed (Neal, 2016; Simola et al., 2010; Sweetman, 2009).

H. PERGOLIDE

Pergolide chemical structure can be seen below:



Pergolide

Figure 10: Pergolide chemical structure (Simola *et al*., 2010).

Pergolide is an ergot derivate drug that functions as a dopamine agonist in Parkinson's disease treatment. It activates dynamine D1 and D2 postsynaptic receptors. Pergolide can be used as a monotherapy for the management of Parkinson's disease early symptoms and also can be used as an adjuvant therapy for L-Dopa with the aim of reducing "end-of-dose" or "on-off" fluctuations from L-Dopa. Pergolide is more commonly used, mainly because it can be used as a monotherapy to postpone L-Dopa or levodopa therapy (Seeman, 2015; Sweetman, 2009; Wagner, 2008).

Pergolide dose used for Parkinson's disease treatment starts from 0.05 mg / day and can be increased up to 0.05-0.15 mg / day for several days until several weeks with a maintenance dose of 0.5-1 mg three times a day, with a maximum dose of 5 mg a day. The side effects reported are almost the same as the side effects from bromocriptine. The highest incidence of side effect reported are sleep attacks and heart failure. Pharmacokinetics of pergolide are described as follows (Montastruc et al., 2016; Simola et al., 2010; Sweetman, 2009; Wagner 2008):

- Pergolide is absorbed in gastrointestinal tract.
- Protein plasma bind : 90%.
- Excretion : mainly through urine in its metabolite form.

I. BROMOCRIPTINE AND PERGOLIDE

Bromocriptine is not commonly used because there is an increased risk pulmonary fibrosis and might reduce its efficacy compared to other dopamine agonists, especially from non-ergot class. Meanwhile, pergolide was initially better than bromocriptine as monotherapy in

Parkinson's disease because it can stimulate 2 dopamine receptors, thereby it can postpone L-dopa (levodopa) treatment. However, it was found that Pergolide is also not commonly used. This is because pergolide is associated cardiac valve diseases. Pergolide has a strong agonist effect on the 5HT2B receptor of the heart, which stimulates fibroblasts and then followed by pulmonary hypertension and / or valve damage, leading to heart failure. A study conducted by Monstruc et al. (2016) reported that ergot derivate dopamine agonist, especially pergolide, caused heart failure [ROR = 4.66 (3.72-5.58), p <0.0001]. This is considered rare, but according to Neal (2016) heart valve diseases associated with pergolide occur in 30% of patients, thereby making pergolide no longer available on the market. This result was also reported in 2007, leading to withdrawal and removal of pergolide from U.S market (Delong and Juncos, 2010; Montastruc et al., 2016; Neal, 2016; Sweetman, 2009; Wells et al., 2009).

Thus, dopamine agonist drug that can be used safely and effectively currently as a treatment for Parkinson's disease as a mild-moderate monotherapy or as an adjuvant therapy of L-dopa (levodopa) is a non-ergot dopamine agonist drug such as Apomorphine, Ropinirole, Pramipexole. This is its selectiveness towards dopamine D2 and D3 receptors and no side effects that causes heart failure (Delong and Juncos, 2010; Neal, 2016; Montastruc et al., 2016; Sweetman, 2009; Wells et al., 2009).

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