

# PHARMACY BULLETIN HOSPITAL KUALA KUBU BHARU

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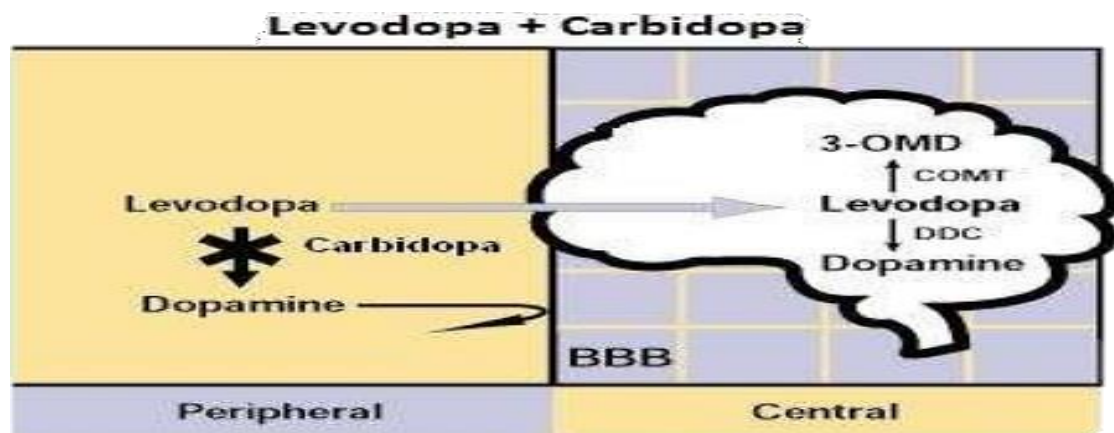
# Long Term Treatment of Levodopa/Carbidopa for Parkinson Disease: Risk of Dyskinesia

## PARKINSON DISEASE (PD)

Parkinson's disease is a brain disorder that causes **unintended or uncontrollable movements**, such as shaking, stiffness, and difficulty with balance and coordination. Symptoms usually begin gradually and worsen over time. As the disease progresses, people may have difficulty walking and talking. They may also have **mental and behavioral changes, sleep problems, depression, memory difficulties, and fatigue**.

## MECHANISM OF ACTION OF LEVODOPA/CARBIDOPA IN THE TREATMENT OF PARKINSON DISEASE

In the central nervous system (CNS) and peripherally, **L-dopa is converted by L-amino acid decarboxylase (L-AAD) to dopamine**. The influx of dopamine created by levodopa helps treat the motor symptoms of PD. In the periphery, **carbidopa will block L-AAD**, prevents the breakdown of levodopa in the bloodstream, thus increasing **CNS penetration of administered L-dopa**. Carbidopa also reduce some of levodopa's side effects such as nausea, cardiac arrhythmias, postural hypotension, and vivid dreams by **decreasing dopamine adverse effects** [1]



## CAUTION

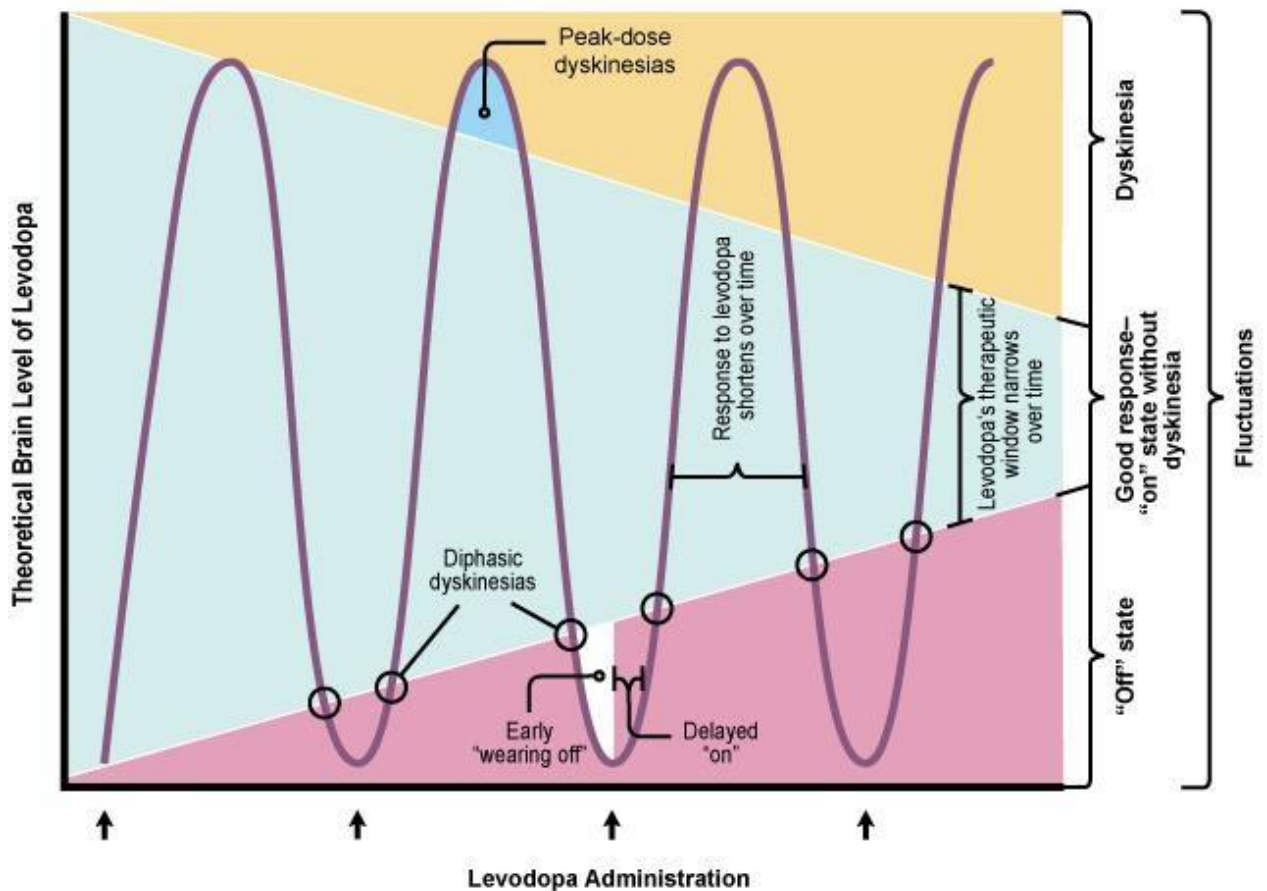


- L-dopa is absorbed primarily in the proximal duodenum via a saturable large neutral amino acid transport system;
- thus, absorption of levodopa may be decreased with high- fat, high calorie, or high-protein meal [1].
- Because protein interferes with the absorption of carbidopa-levodopa, take the medication either 30 minutes before or one to two hours after a meal.



## Long-term L-dopa/carbidopa treatment

- After 5 years most of these patients suffer loss of efficacy, dyskinesias, fluctuations, or toxicity [3].
- Dyskinesias, involuntary choreiform movement usually involving the neck, trunk, and extremities, are usually associated with peak striatal dopamine levels [4].
- Based on the temporal pattern in relationship to L-dopa dosing, they are divided into
  - i. "peak-dose dyskinesia" – the most common.
  - ii. "diphasic dyskinesia".
  - iii. "wearing off" or "off-period" dyskinesia.



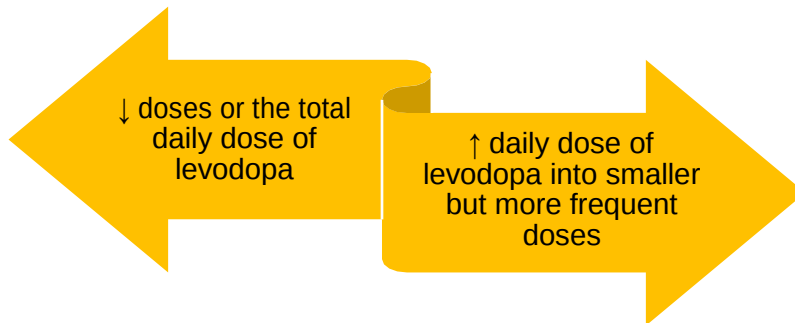
## Case Study

- An 82-year-old female patient reported of experienced generalized dyskinesia after taking L-dopa/carbidopa for 15 years.
- During admission, she had poor oral intake, loss of appetite (LOA), and unable to tolerate orally. She has no known drug allergies.
- Medical illness: diabetes mellitus, hypertension, dyslipidaemia, and PD.
- Her oral L-dopa/carbidopa was 250/25 mg TDS.
- After dyskinesia symptoms were observed, her L-dopa/carbidopa was discontinued and she was treated with oral risperidone. Then, dyskinesia symptoms were resolved.
- The dose was reduced to 125/12.5 mg QID but dyskinesia symptoms was presented. L-dopa/carbidopa was discontinued. No symptoms of dyskinesia was observed until discharged.

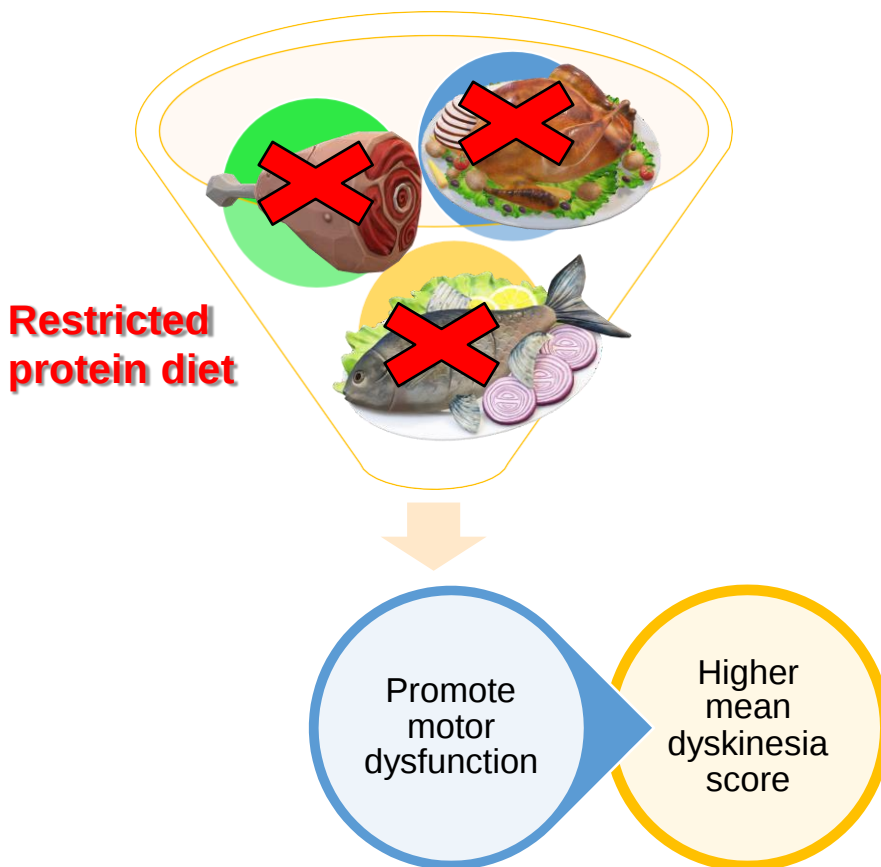


## Management of established L-dopa induced dyskinesia

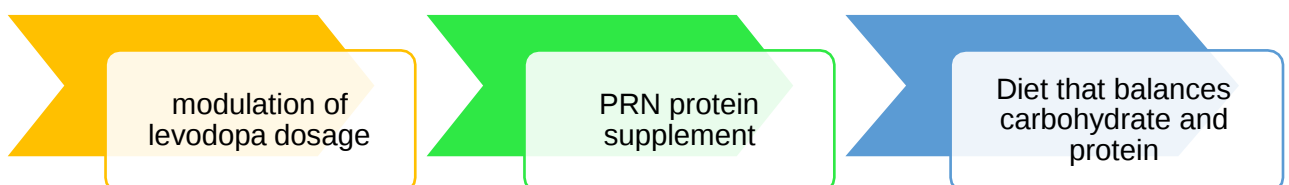
↓ severity of peak dose dyskinesia by:



### Dietary Intake and bioavailability of L-dopa



### Reducing the risk of motor dysfunction or dyskinesia



References: [1] Wells, B. G., Schwinghammer, T. L., DiPiro, J. T., & DiPiro, C. V. (2017). Parkinson disease. In M. Weitz & B. Kearns (Eds.), *Pharmacotherapy handbook* (10th ed., pp. 587-596). United States of America: McGraw-Hill Education. Lee, C. S. (2001). Levodopa-induced dyskinesia: Mechanisms and management. *BCMJ*, 43(4), 206-209. [3] Marsden, C.D., J.D. Parkes, and N. Quinn, 7 - *Fluctuations of disability in Parkinson's disease – clinical aspects*, in *Movement Disorders*, C.D. Marsden and S. Fahn, Editors. 1981, Butterworth-Heinemann. p. 96-122. [4] Vijayakumar, D. and J. Jankovic, *Drug-Induced Dyskinesia, Part 1: Treatment of Levodopa-Induced Dyskinesia*. *Drugs*, 2016. **76**(7): p. 759-77. [5] Marsden, C.D., J.D. Parkes, and N. Quinn, 7 - *Fluctuations of disability in Parkinson's disease – clinical aspects*, in *Movement Disorders*, C.D. Marsden and S. Fahn, Editors. 1981, Butterworth-Heinemann. p. 96-122.

# MAJOR DEPRESSIVE DISORDER

PREPARED BY : VINOSHINI A/P PONNIAH

## WHAT IS MAJOR DEPRESSIVE DISORDER (MDD)



## TYPES OF MAJOR DEPRESSION DISORDER

Major depressive disorder is also known as Clinical depression. SEVERE FORM OF DEPRESSION <sup>1</sup>.

Major depressive disorder impacts a person's:

- Mood
- Cognition
- Behaviour



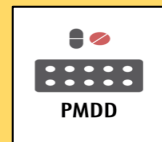
Postpartum Depression



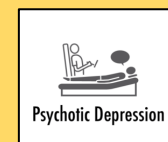
Bipolar Depression



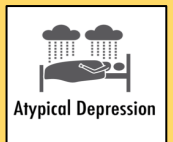
Seasonal Affective Disorder



PMDD



Psychotic Depression



Atypical Depression

**OTHER TYPES:**  
-MELANCHOLIC DEPRESSION  
-CATATONIC DEPRESSION  
--PERSIST DESPITE DISORDER

## EFFECTS OF DEPRESSION ON THE BRAIN <sup>3</sup>

### STRUCTURAL & CONNECTIVE CHANGES



#### LEADS TO:

- memory impairment.
- can result in preventing the person from getting things done (executive function) and affect their attention.
- Can directly affect mood and emotional regulation.

### BRAIN SHRINKAGE



#### LEADS TO:

- Loss of grey matter volume (GMV- tissue with a lot of brain cells). Lower GMV in these certain areas at brain can cause :
- Memory problems
  - Trouble thinking
  - Hopelessness
  - Sleep or appetite problems
  - Anxiety

### BRAIN INFLAMMATION



#### LEADS TO DEAD OF BRAIN CELLS:

- This lead to complications:
- Brain shrinkage
  - decreased function of neurotransmitters
  - neuroplasticity

# CLINICAL PRESENTATIONS<sup>2</sup>

Isolation

Thoughts of death

No appetite

Sadness

No energy



Sleep disturbance

Guilt

Anger

Dependence

No concentration



## NON-PHARMACOLOGICAL TREATMENT<sup>1</sup>



Psychotherapy



Sleep minimum 8 hours



Art or music therapy



Yoga



Aerobic exercises



Cognitive behavioural therapy or Interpersonal therapy

## NOTE: DANGER OF MDD<sup>2</sup>

-PERSISTENT (CAN LAST FROM DAYS TO YEARS)

-MAINLY AFFECTS DAILY LIVING

-SUICIDAL THOUGHTS!!!



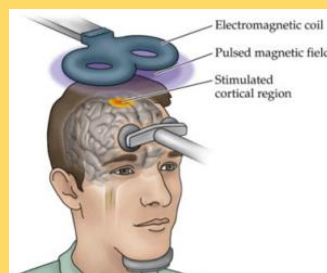
# PHARMACOLOGICAL TREATMENT<sup>1</sup>

|                                                                                                           |                                                                                     |                                                                                                             |
|-----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
|                          |    |                           |
| <b>Selective Serotonin Uptake Inhibitors- SSRIs</b><br>(e.g. Setraline)                                   | <b>Multimodal Serotonin Modulator</b><br>(e.g : Vortioxetine)                       | <b>Selective Serotonin And Norepinephrine Reuptake Inhibitor (SNRI)</b><br>(e.g.: Desvenlafaxine Succinate) |
|                          |    |                          |
| <b>Noradrenergic-Specific Serotonergic Antidepressants</b><br>( e.g. Mirtazapine)                         | <b>Monoamine Oxidase Inhibitors</b><br>(e.g Selegiline)                             | <b>Tricyclic Antidepressants</b><br>(e.g. Amitriptyline)                                                    |
|                        |  |                         |
| <b>Atypical Antidepressants- Melatonergic Agonist &amp; Serotonergic Antagonist</b><br>(e.g. Agomelatine) | <b>Noradrenaline /Dopamine Reuptake Inhibitor</b><br>(e.g : Bupropion)              | <b>Short Term Use Of Anti-Anxiety Medications</b><br>(e.g. Benzodiazepines: Clonazepam, Alprazolam)         |

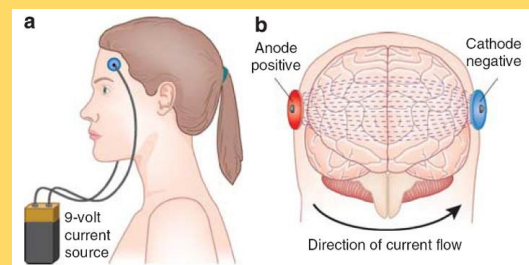
## PHYSICAL TREATMENT<sup>1</sup>



Electroconvulsive therapy (ECT)



Transcranial magnetic stimulation (TMS)



Transcranial Direct Current Stimulation

### References:

1. CPG Management of Major Depressive Disorder\_(Second Edition) 2019
2. <https://www.webmd.com/depression/depression-physical-effects-brain>
3. <https://www.healthline.com/health/depression-physical-effects-on-the-brain>

# PROGYLUTON®

## as a Hormone Replacement Therapy (HRT)



### 1. What is hormone replacement therapy?

Hormone replacement therapy (HRT) is supplementing women with hormones lost during the menopausal transition, which to relieve the symptoms associated with menopause <sup>(1)</sup>

### 2. What are the symptoms of menopause?



Hot Flashes



Night Sweat



Vaginal Dryness



Urinary incontinence



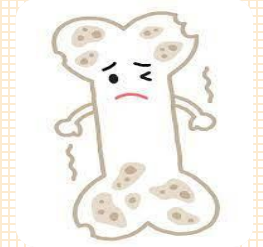
Emotional Changes



Sleep disturbance



Decreased sexual desire



Bone Thinning

### 3. What are the types of hormone therapy?

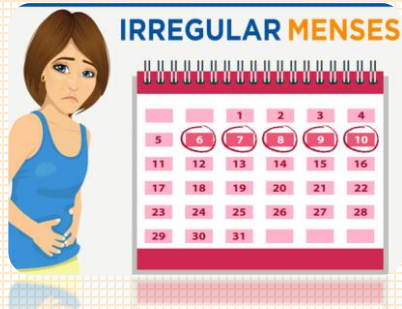


**Estrogen Therapy:** Estrogen is taken alone. Doctors most often prescribe a low dose of estrogen to be taken as a pill or patch every day. Estrogen may also be prescribed as a **cream, vaginal ring, gel or spray**. You should take the lowest dose of estrogen needed to relieve menopause symptoms and/or to prevent osteoporosis. Example of estrogen therapy are **estradiol** <sup>(4)</sup>

**Estrogen Progesterone/Progestin Hormone Therapy (EPT):** Also called combination therapy, this form of HT combines doses of estrogen and progesterone (or progestin, a synthetic form of progesterone). Example of EPT is **levonorgestrel + ethinylestradiol** <sup>(4)</sup>

## 4. What is Progyluton?

- ❖ Progyluton contains **Estradiol Valerate (Estrogen)** and **Norgestrel (Progesterone)** as active ingredients. <sup>(5)</sup> Progyluton is indicated for **pre and post menopausal syndrome, primary and secondary amenorrhea, menstrual irregularities and deficiency symptoms after oophorectomy or radiological castration for noncarcinomatous disease.** <sup>(6)</sup>



## 5. How Progyluton works?

Primarily, it **prevent ovulation** (the release of an egg from an ovary), other alterations include **changes in the cervical mucus** (which **increase the difficulty of sperm entry into the uterus**) and the **endometrium** (which **reduce the likelihood of implantation**) <sup>(7)</sup>



## 6. How to take Progyluton?



- If still menstruating, treatment should begin on the 5th day of menstrual bleeding <sup>(8)</sup>
- If having irregular period, may start at any time, provided pregnant has been excluded <sup>(8)</sup>



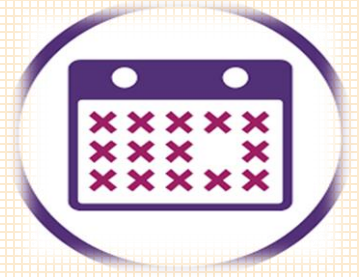
## 7 What is the dosage of Progyluton?

- ❖ There are **2 colours of tablets** which is **white and light brown colour** <sup>(8)</sup>
- ❖ **1 white tablet need to be taken daily for the first 11 days**, followed by **1 light brown tablet daily for next 10 days to complete for 21 days** <sup>(8)</sup>
- ❖ After completed 21 days, there will be **tablet-free interval of 7 days** <sup>(8)</sup>



## 8. What if I missed my dose?

- ✓ Should be taken as soon as possible within following 12 hours in case forgot to take the tablet <sup>(6)</sup> <sup>(8)</sup>
- ✓ If more than 24 hours, no extra tablets need to be taken <sup>(8)</sup>



## 9. What is the common side effect?



Weight gain or weight loss



Rash or pruritus



Abdominal pain



Headache



Vaginal or uterine bleeding



Nausea

### References:

1. Harper-Harrison, G. and Shanahan, M.M., 2021. Hormone Replacement Therapy. *StatPearls [Internet]*.
2. Nanette Santoro, Cassandra Roeca, Brandilyn A Peters, Genevieve Neal-Perry, The Menopause Transition: Signs, Symptoms, and Management Options, *The Journal of Clinical Endocrinology & Metabolism*, Volume 106, Issue 1, January 2021, Pages 1–15, <https://doi.org/10.1210/clinem/dgaa764>
3. <https://www.rcog.org.uk/en/patients/menopause/hrt-and-alternatives/>
4. <https://my.clevelandclinic.org/health/treatments/15245-hormone-therapy-for-menopause-symptoms>
5. <https://www.tabletwise.net/uae/progyluton-tablet>
6. KKM Formulary
7. <https://www.drugs.com/pro/norgestrel-and-ethinyl-estradiol.html>
8. Progyluton Product Leaflet

Prepared by: Anis Fitriah Binti Azhar

# Levothyroxine in

## Hashimoto disease



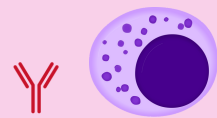
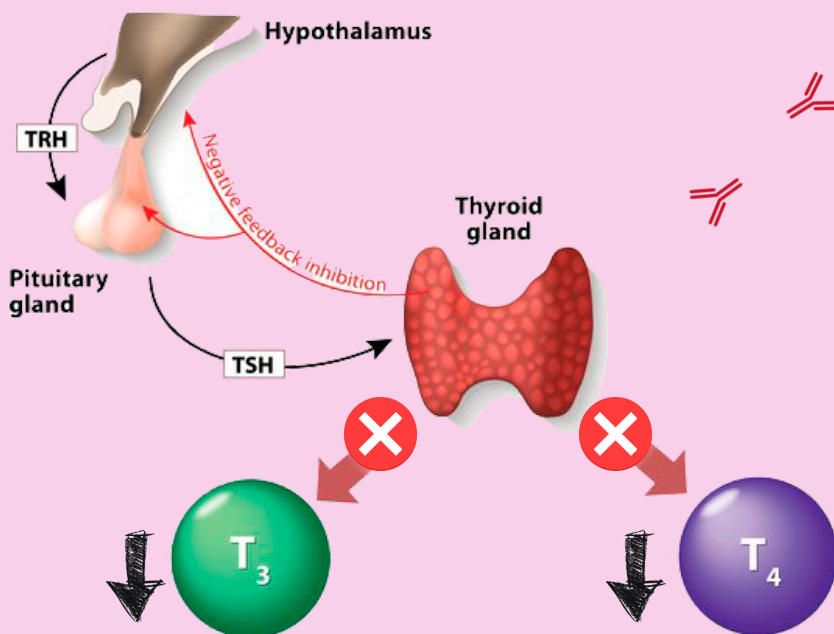
by Nurul Aisyah binti Amran

### What is Hashimoto Disease? (1)(3)(4)

Hashimoto Thyroiditis is an autoimmune disease that leads to a gradual loss of thyroid function. Hashimoto is one of the most common factors that cause primary hypothyroidism. The prevalence of Hashimoto disease increases with age.

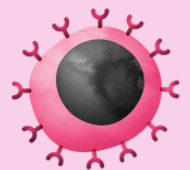
In Hashimoto disease, the immune system produces antibodies against the thyroid antigen such as thyroid peroxidase (TPO) and TSH receptor. Both antigens are essential in thyroid hormone production (Levothyroxine (T<sub>4</sub>) and Triiodothyronine (T<sub>3</sub>) hormones)

### Pathogenesis of Hashimoto disease (1)(3)(4)



#### B cell role

- Produce thyroid antibodies against thyroid peroxidase (TPO) and TSH receptor.
- TPO antibodies inhibit TPO enzyme activity



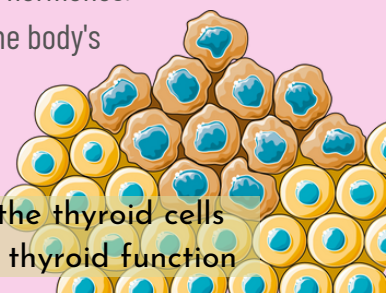
#### T cell role

- Th2 helper cells help to enhance antibody production
- Apoptotic destruction of thyroid cells by activating cytotoxic T cells

**TRH** - Thyroid Releasing Hormone  
**TSH** - Thyroid Stimulating Hormone  
**T<sub>3</sub>** - Triiodothyronine hormone  
**T<sub>4</sub>** - Thyroxine hormone

- Damaged thyroid gland and interruption of thyroid hormone production by these autoimmune causes low T<sub>3</sub> and T<sub>4</sub> hormones.
- Thyroid hormones function is important in regulating the body's metabolism and growth.

Autoantibodies damage the thyroid cells leading to gradual loss of thyroid function



## Sign and symptoms of Hashimoto disease <sup>(7)</sup>

Dull facial expressions, fatigue, confusion, droopy eyelids, puffy and swollen face, sides of eyebrows fall out

Increased or irregular menstrual flow in women.

Dry hair and dry skin

Intolerance to cold

Excessive weight gain

Constipation

Muscle cramps



## Monitoring lab parameters <sup>(5)(6)</sup>

In Hashimoto, there is the presence of high serum concentrations of antibodies to thyroid peroxidase (TPO) and thyroglobulin (Tg)

**TPO antibody test**

*Positive*

**Thyroglobulin antibody (TgAb)**

*Positive*

**Thyroid Stimulating Hormone, TSH**

*High (Ref range: 0.35 - 5.5 mU/L)*

**Free thyroxine, FT4**

*Low (Ref range: 11.8 - 23.2 pmol/L)*



## Complications <sup>(7)</sup>

- **Goiter**
  - Low level of thyroid hormone causes the enlargement of the thyroid gland in order to compensate for it.
- **Heart problems.**
- **Mental health issues**
  - Depression may occur.
  - Low sexual desire (libido) can lead to slowed mental functioning.
- **Myxedema coma.**
  - Rare, life-threatening condition can develop due to long-term severe untreated hypothyroidism
- **Birth defect**



# Treatment: Levothyroxine, T4

## Mechanism of action<sup>(2)</sup>

- Levothyroxine (T4) is a synthetic form of thyroxine, an endogenous hormone secreted by the thyroid gland. T4 is converted to its active metabolite, L-triiodothyronine (T3).
- Thyroid hormones (T4 and T3) then bind to thyroid receptor proteins in the cell nucleus and exert metabolic effects through control of DNA transcription and protein synthesis; involved in normal metabolism, growth, and development; promotes gluconeogenesis, increases utilization and mobilization of glycogen stores, and stimulates protein synthesis, increases basal metabolic rate.

## Levothyroxine in HKKB



Levothyroxine 25 mcg



Levothyroxine 50 mcg



Levothyroxine 100 mcg

## Dose<sup>(2)</sup>



Adjust initial dose by 12 to 25 mcg/day every 3 to 6 weeks based on clinical response and serum TSH and/or free T4 concentrations until TSH is normalized at a stable dose for  $\geq 6$  weeks.

## Administration<sup>(2)</sup>

Administer consistently in the morning on an empty stomach, at least 30 to 60 minutes before food. Alternatively, may consistently administer at night 3 to 4 hours after the last meal

## Pregnancy and breastfeeding<sup>(2)</sup>



Levothyroxine has not been shown to increase the risk of congenital abnormalities or miscarriage; however, normal levels of maternal thyroid hormones are required for fetal development.

Adequate thyroid hormone concentrations are required to maintain normal lactation.

## Side effects<sup>(2)</sup>

Adverse reactions are primarily those of hyperthyroidism due to therapeutic overdosage.

- |                            |                           |
|----------------------------|---------------------------|
| • flushing                 | • vomiting                |
| • increased blood pressure | • Increased liver enzymes |
| • increased pulse          | • fatigue                 |
| • tachycardia              | • headache                |
| • Alopecia                 | • heat intolerance        |
| • weight loss              | • diarrhea                |

## REFERENCE:

- 1) UpToDate: Pathogenesis of Hashimoto's thyroiditis (chronic autoimmune thyroiditis)
- 2) UpToDate: Levothyroxine Drug Information
- 3) <https://u.osu.edu/hashimoto/pathophysiology-and-clinical-presentation-correct-diagnosis/>
- 4) <https://www.elsevier.es/en-revista-endocrinologia-nutricion-english-edition-412-pdf-S2173509316300757>
- 5) <https://www.verywellhealth.com/how-to-test-for-hashimotos-disease-4159884#:~:text=If%20your%20TSH%20level%20falls,that%20you%20may%20have%20hypothyroidism.>

- 6) <https://medlineplus.gov/lab-tests/thyroid-antibodies/>
- 7) <https://www.mayoclinic.org/diseases-conditions/hashimotos-disease/symptoms-causes/syc-20351855#:~:text=Hypothyroidism%20can%20result%20in%20poor,cardiovascular%20disease%20and%20heart%20failure.>