

Neuropsychiatric Aspects of Endocrine Disorders

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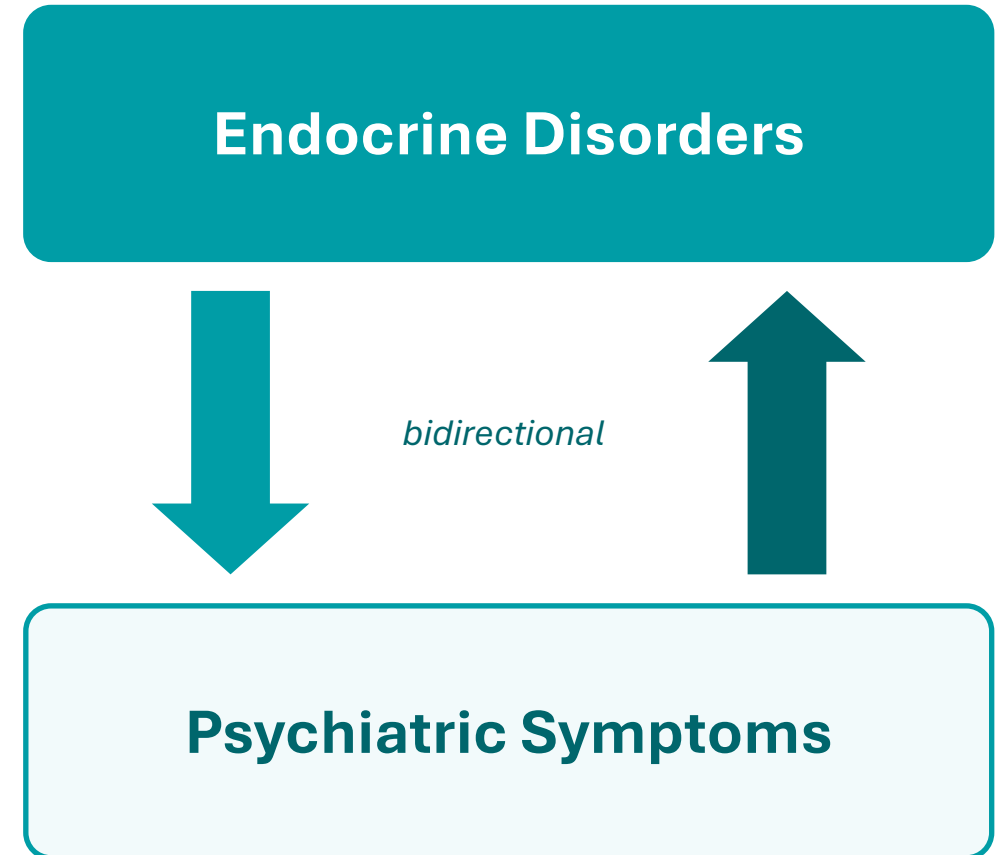
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Neither I nor my spouse have a relevant
financial relationship with a commercial interest to disclose

Objectives

- 1) Understand the bidirectional relationship between endocrine conditions and psychiatric symptoms.
- 2) Review the most common endocrine disorders that can lead to psychiatric symptoms.



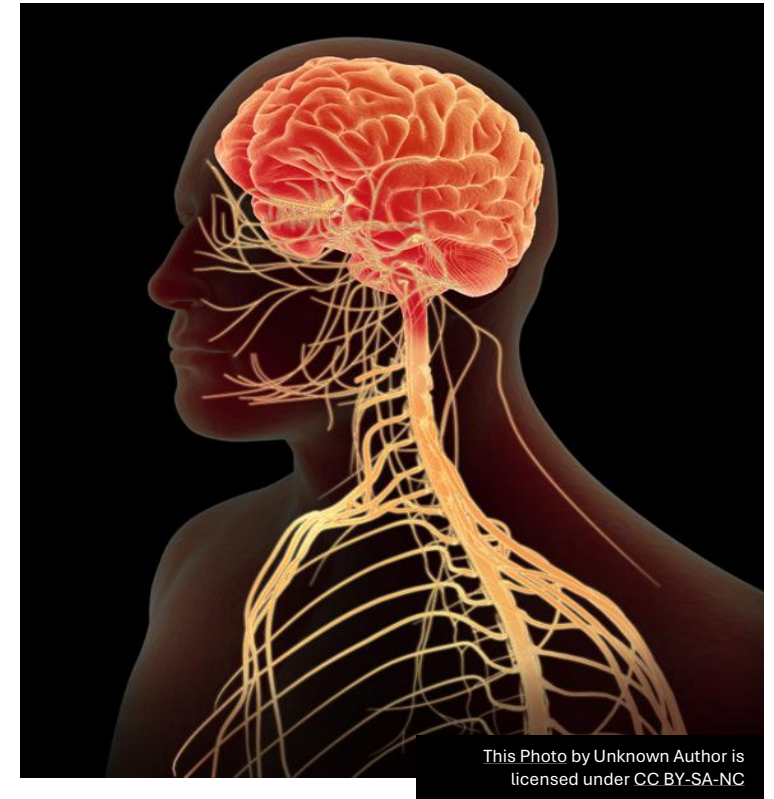
Topics:

1. Endocrine Disorders

- Thyroid
- Parathyroid
- Pituitary
- Adrenals

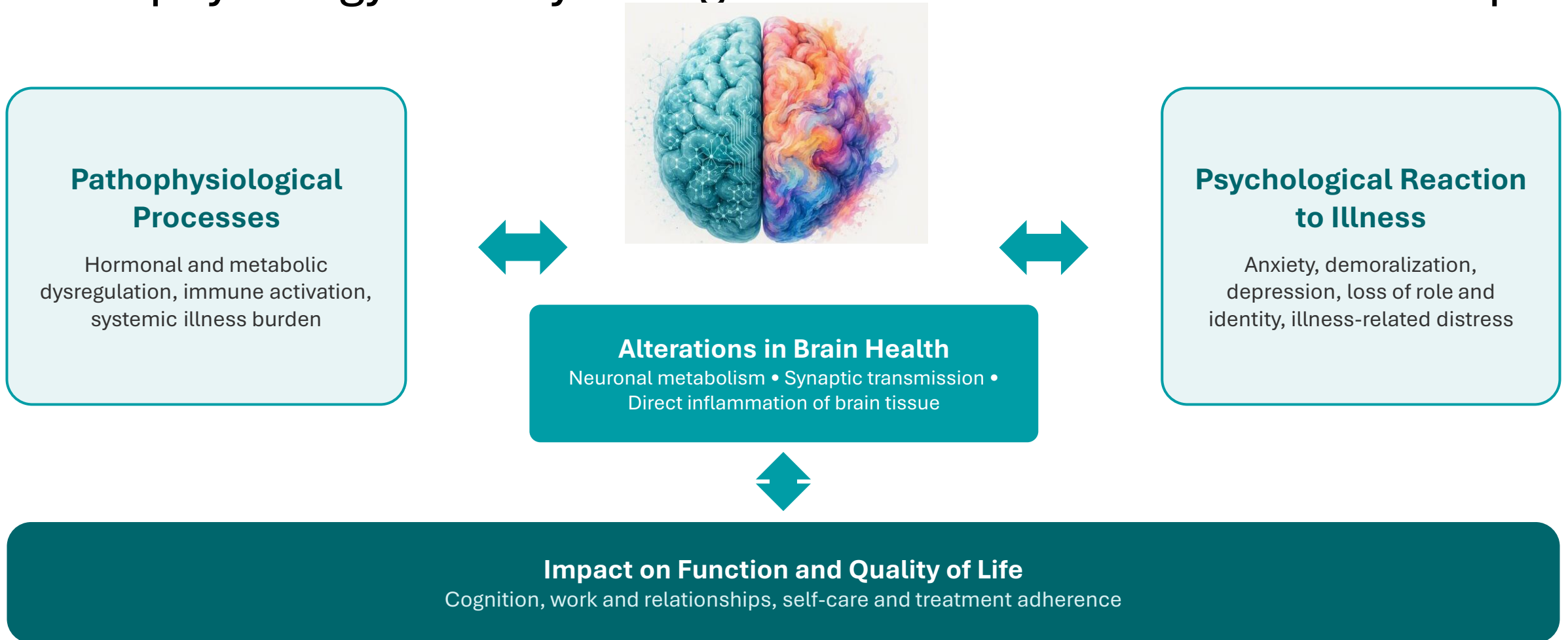
2. Diabetes

- DM and depression
- DM and cognition
- Hypoglycemia



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Pathophysiology and Psychological Reactions: A Bidirectional Loop



Each pathway feeds the other: treating only one side of the loop leaves the cycle intact.

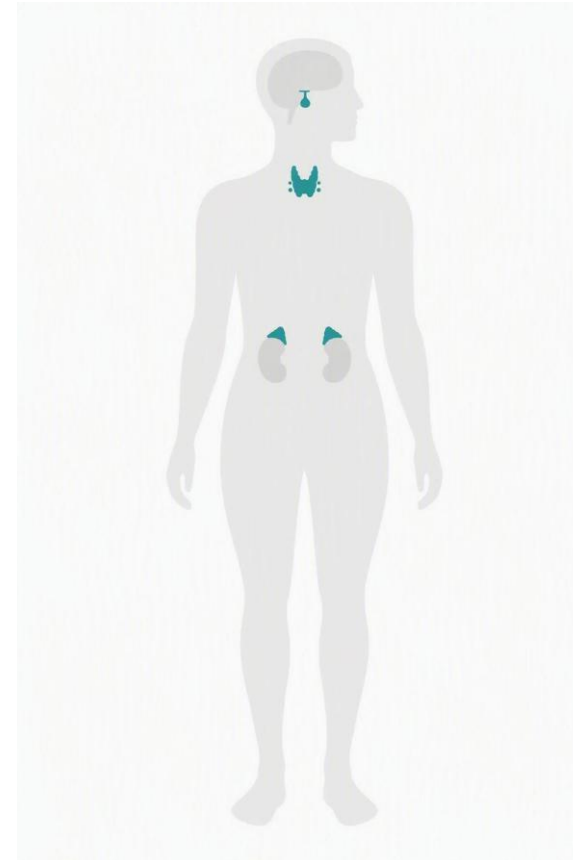
Endocrine Disorders

Thyroid

Parathyroid

Pituitary

Adrenals





Brigham and Women's Hospital
Founding Member, Mass General Brigham

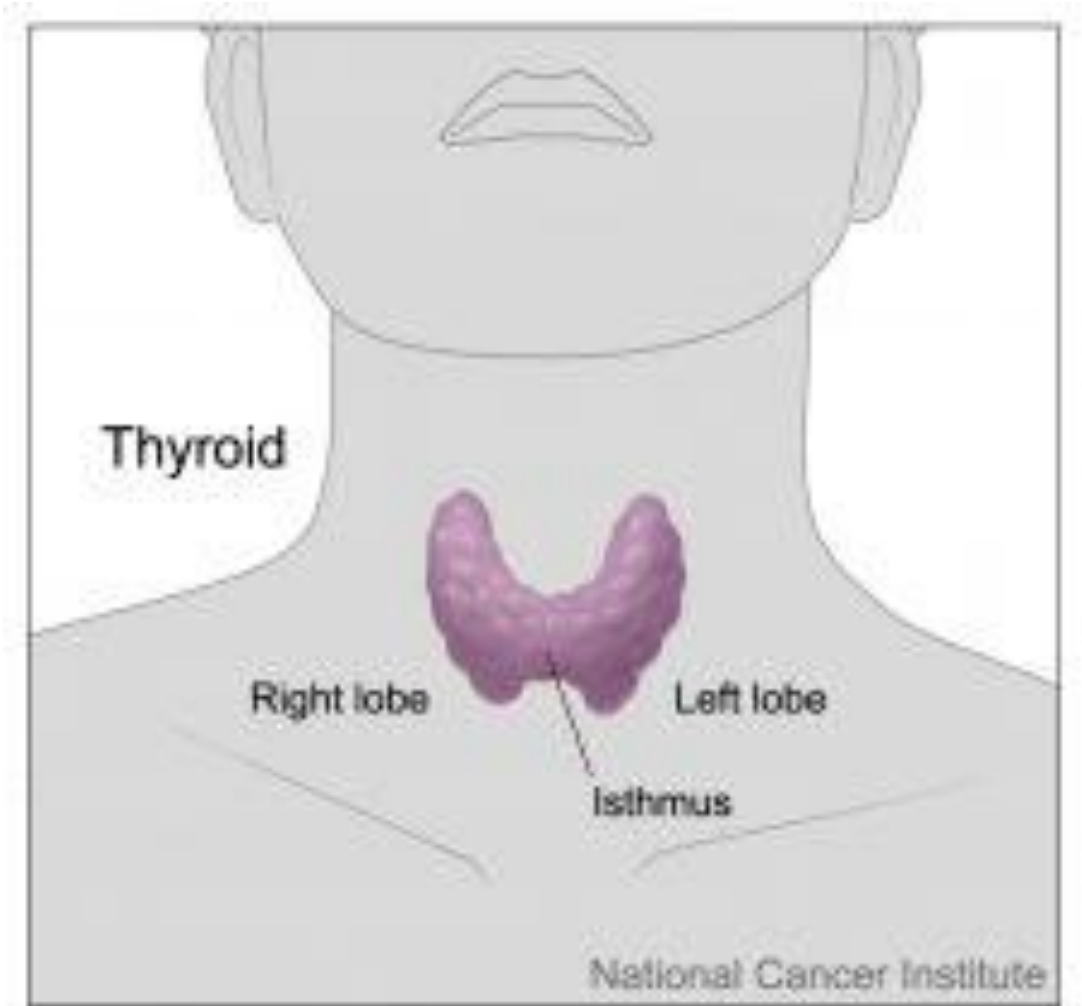


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Disorders of the Thyroid

Common, routinely screened, and often reversible

The link has been recognized since the 1800s, when clinicians noted psychosis in patients with advanced myxedema.



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Case 1: 50 y/o F with MDD, recent increase in anxiety, depression.



- PMHx: DM2, Obesity, OSA, h/o Gastric bypass, Anemia, Breast CA (remission).
- Employed– episodes (both physical/emotional), led to multiple LOA's, need for intensive outpatient psychiatric care.
- Seen in our clinic for months– no improvement. Medical w/u done: Undetectable TSH, Free T4: 5.2 (H).
- E-consult Endocrine, further labs sent (total T3, TPO, Thyroglobulin, TSI/TBII).
- Diagnosis: Graves Disease. Methimazole started.

Disorders of the Thyroid:

 **Brigham and Women's Hospital**
Founding Member, Mass General Brigham



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Hyperthyroidism

Hyperthyroidism (Thyrotoxicosis)

Neuropsychiatric & Cognitive

- Anxiety
- Mixed affective state (euphoria, lability) and increased activity
- Psychosis
- Cognitive impairment: reduced attention and concentration, impaired recall, rapid speech
- Delirium
- Insomnia

Physical

- Heat intolerance
- Atrial fibrillation, heart failure
- Weight loss, fatigue, weakness
- Hyperactive reflexes, muscle wasting
- Frequent bowel movements
- Amenorrhea or irregular periods
- Hair loss
- Warm skin

Hyperthyroidism

Primary

- Most common in women
- Most common cause is Grave's disease
- TSH is low and fT4 is high

Central or Secondary Thyrotoxicosis

- Rare
- TSH is nonsuppressed, Free T4 is normal or high and T3 is high
- Pituitary adenoma

Subclinical Hyperthyroidism

- TSH is low and Free T4 and T3 are normal
- In most cases, TSH should be repeated in 2 weeks–3 months depending on levels/symptoms
- TSH <0.1 mIU/L needs treatment for hyperthyroidism even if no typical clinical symptoms of thyrotoxicosis
- Consider tx in pts who are symptomatic, >65 y/o or those with underlying cardiac disorders



Disorders of Thyroid

Hypothyroidism (Myxedema)

- Gradual onset and slow progression especially in the elderly. Common (5/100, F>M).
- Different from Alzheimer's and Frontotemporal dementia because it does not have cortical dysfunction (aphasia, anomia, apraxia, frontal disinhibition)
- More commonly admitted for depression and bipolar symptoms



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Hypothyroidism (Myxedema)



Neuropsychiatric & Cognitive

- Depression, mania, mood swings
- Apathy or irritability
- Psychosis (myxedema madness, up to 10%)
- **Cognitive impairment:** slow comprehension, inattention, poor recent memory and abstract thinking, slow speech
- Delirium
- Susceptibility to sedatives and anticholinergics
- Low energy
- Sleep disturbances: hypersomnia, sleepiness, worsening of sleep apnea

Physical

- Cold intolerance
- Edema
- Weight gain
- Constipation
- Amenorrhea or irregular periods
- Hair loss
- Cool, dry skin
- Hoarse voice
- Muscle stiffness, delayed relaxation phase of reflexes

Hypothyroidism

Primary Hypothyroidism

- ↑TSH / low fT4: dysfunction of the thyroid gland itself

Secondary or Tertiary Hypothyroidism

- TSH below normal/normal with low fT4: pituitary or hypothalamic dysfunction

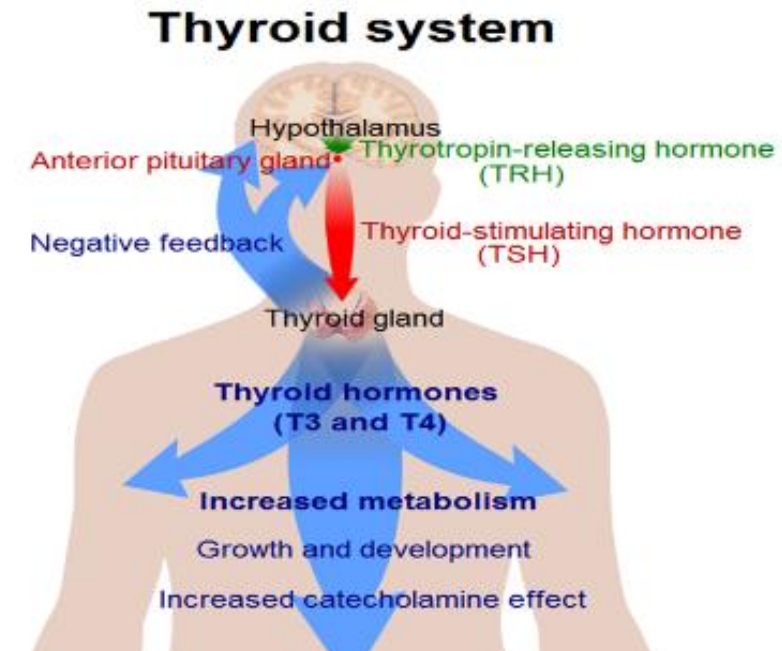
Subclinical Hypothyroidism

- ↑serum TSH, with normal levels of FT4
- Increased risk for atherosclerosis, cardiac events
- Increased risk of cognitive impairment, fatigue, low mood
- Meta-analysis: up to 50% of treatment-resistant depression (TRD) had subclinical hypothyroidism
- Variable outcomes and controversy (absence of large clinical trials) about treating subclinical hypothyroidism in depression
- Most cases can be observed w/out tx. Consider Tx if TSH >10 mU/L or for younger patients



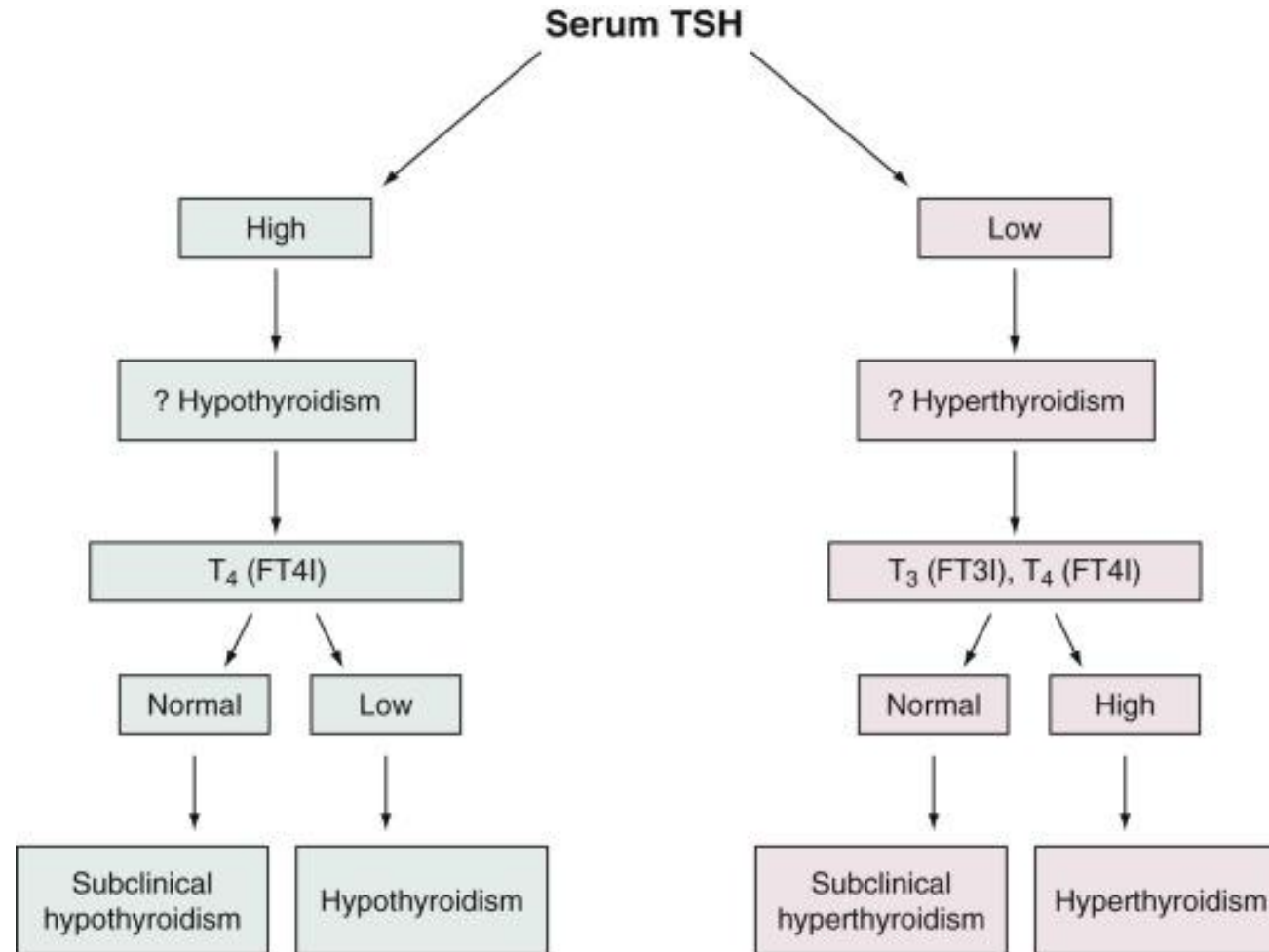
Laboratory tests

- Thyroid stimulating hormone (TSH): pulsatile manner, serum half-life 50 minutes, peak 2–4am, nadir 4–8pm
 - Traditional TSH (0.5–5.0 mU/L)
- T4 constitutes 80% of hormone secreted; when released into circulation, it forms T3 through the process of de-iodination
- Combination is highly sensitive and specific to detect deficiency or excess



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Screening for thyroid disorders



Risk factors for hypothyroidism

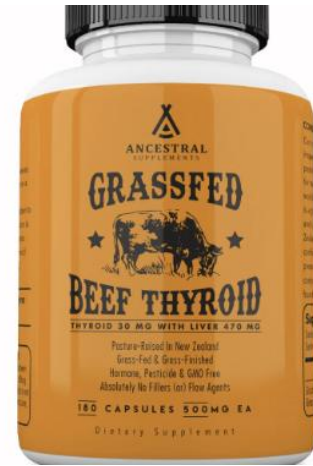
- Older age
- Female gender
- Graves disease
- Hashimoto disease
- Other autoimmune disease (e.g., type 1 diabetes, adrenal insufficiency, vitiligo)
- Post-thyroidectomy
- Goiter
- Prior neck irradiation
- Laryngectomy alone or with external irradiation
- Drugs (lithium, amiodarone, iodine-containing compounds)

Who and when to check thyroid test

- All patients with concerning physical symptoms and signs
- All females over 50 years-old with psychiatric disorders, with/without somatic symptoms/signs at exam
- Refractory conditions
- Individuals older than 65 year-old

Augmentation with Thyroid Hormone

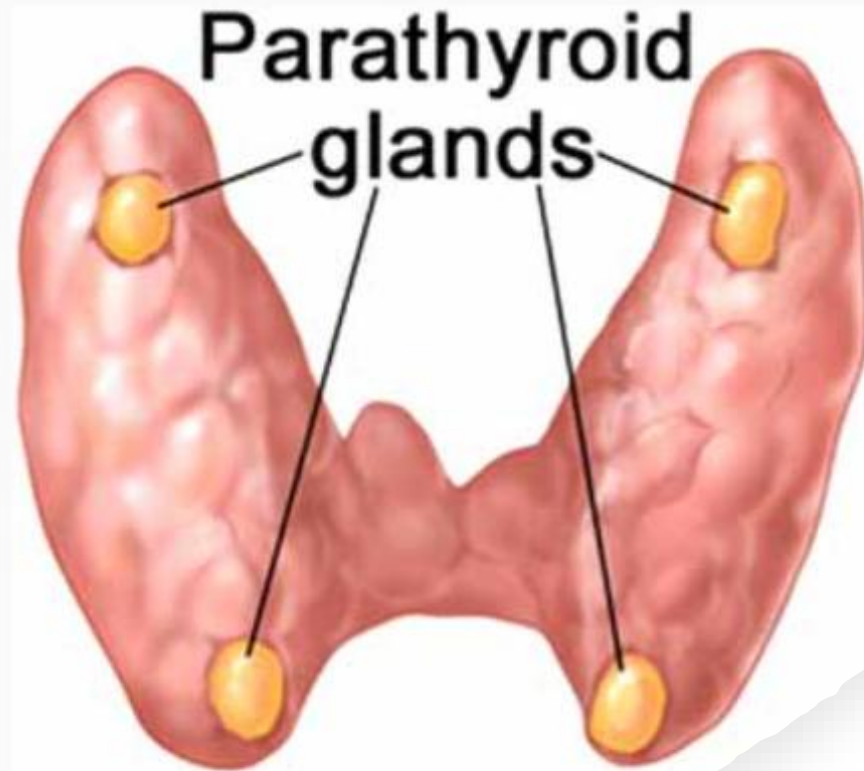
- Add-on/Augmentation strategy for Mood Disorders, depression with associated lethargy and fatigue.
- T3 (most commonly used for mood) and T4 (most commonly used for hypothyroidism).
- Dose: 12.5-50 mg in AM.
- Mechanism? Stimulating metabolism and energy, central therapeutic role affecting brain homeostasis.
- Risks: bone density/osteoporosis, arrhythmias, hyperthyroidism Sx.
- Efficacy is independent of baseline TSH.
- Heard of Desiccated Thyroid? Derived from bovine/porcine thyroid glands (T3/T4→1:4).



Am J Psychiatry. Hormonal Tx for MDD 2020

[FDA: actions to address unapproved thyroid medications](#)

Parathyroid Glands Disorders



Parathyroid Glands Disorders: Hyperparathyroidism

- “Stones, bones, groans and moans”
- Correlation with elevated calcium:
 - Mild (10-12mg/dl), personality changes, irritability, decreased spontaneity and initiative
 - Moderate (12-16 mg/dl), depression, apathy, anxiety, poor concentration and recent memory and sometimes suicidal
 - Severe (16-19 mg/dl), sudden psychosis, disorientation, delusions, hallucinations, paranoia
 - Above 19 mg/dl stupor and coma



Parathyroid Glands Disorders: Hypoparathyroidism

- 30-50% manifest with psychiatric symptoms.
- Can occur after neck surgery, autoimmune, genetic
- Depression, anxiety, irritability, social phobias and obsessions
- More severe cases: confusion, psychosis
- Some series reported intellectual impairment as the major psychiatric finding



Signs and Sx of Hypoparathyroidism, Endocrinol Metab Clin N AM, 2018

Lithium and the Endocrine system

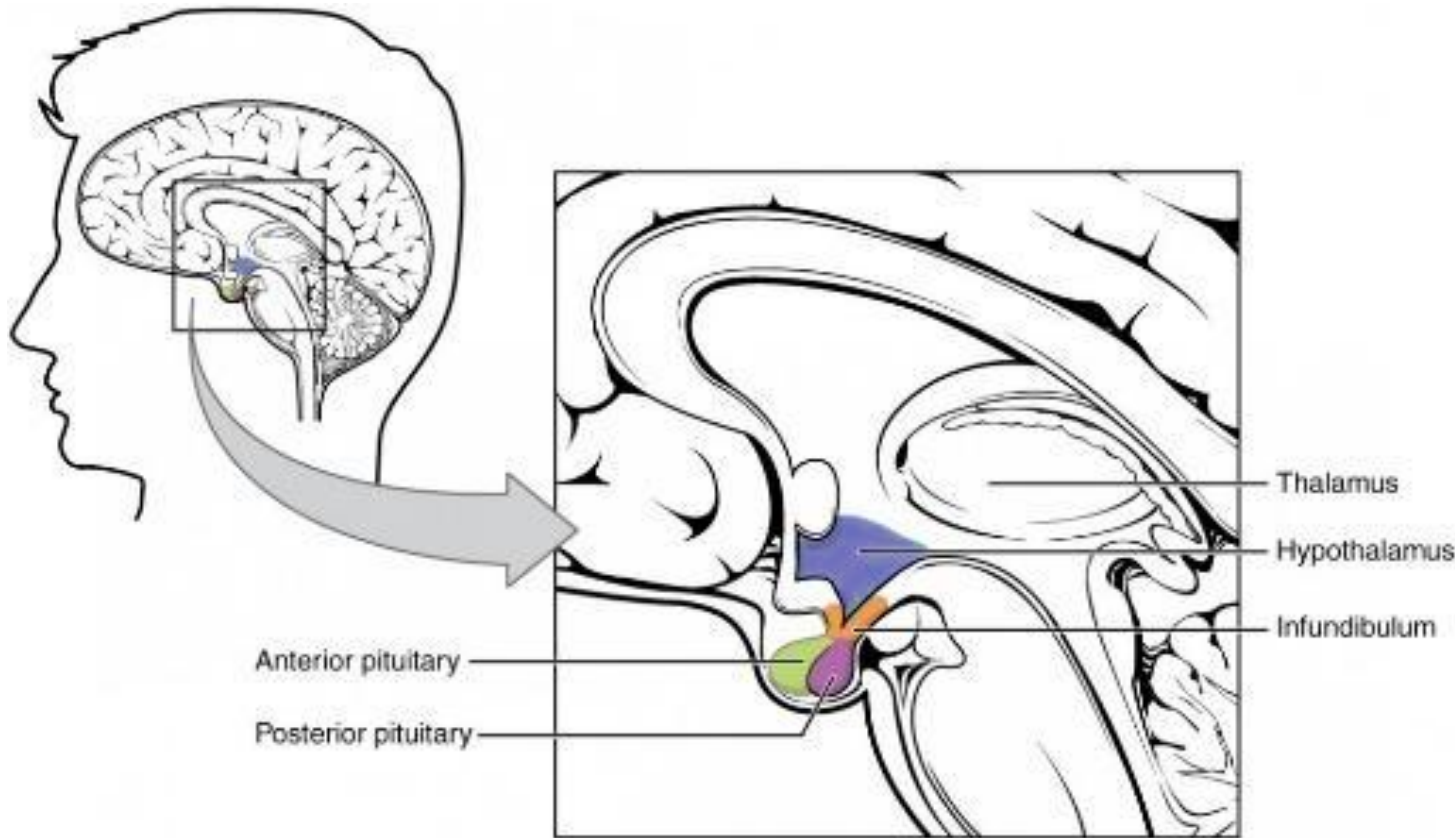


Tips: Monitor regularly, detect early, treat, lowest effective dose, once-daily dosing (kidneys).

- Modulates NT's, Inhibits Inositol MP, GSK-3, alters neuronal sodium transport,  BDNF.
- Can impact Endocrine systems: Thyroid, Parathyroid. Interferes with hormone synthesis, release.
- Thyroid:  T3/T4 (Interfere with Iodine uptake), sensitivity to TSH $\rightarrow$ + goiter, hypothyroidism.
- Parathyroid: Promote growth adenomas, stimulation of PTH, Hypocalciuria related to renal dysfunction, interference with calcium-mediated transmembrane signals



Disorders of Pituitary Function



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- Hypothalamic-pituitary axis connects with CNS structures (prefrontal cortex and limbic system).
- Pituitary hormones control critical gland functions: adrenals, thyroids, gonads.
- Pituitary Adenomas: typically benign, can produce diverse clinical/pathological psychiatric symptoms.

Disorders of Pituitary Function: Hyperpituitarism

Excessive secretion or production of one or more of the hormones produced by the pituitary gland

Prolactinoma: most common (40%)

Somatic: galactorrhea, gynecomastia, amenorrhea, decreased libido/sexual dysfunction

Psychological: hostility, depression, anxiety and apathy

Acromegaly: pituitary adenomas. Physical features, depression, gambling, psychosis, apathy, novelty-seeking behaviors

Psychiatric medications: inhibition of dopamine

Disorders of Pituitary Function: Hypopituitarism

Infundibular-hypothalamic area susceptible to TBI, SAH and tumors (most common).

Most common Growth hormone (GH) deficiency

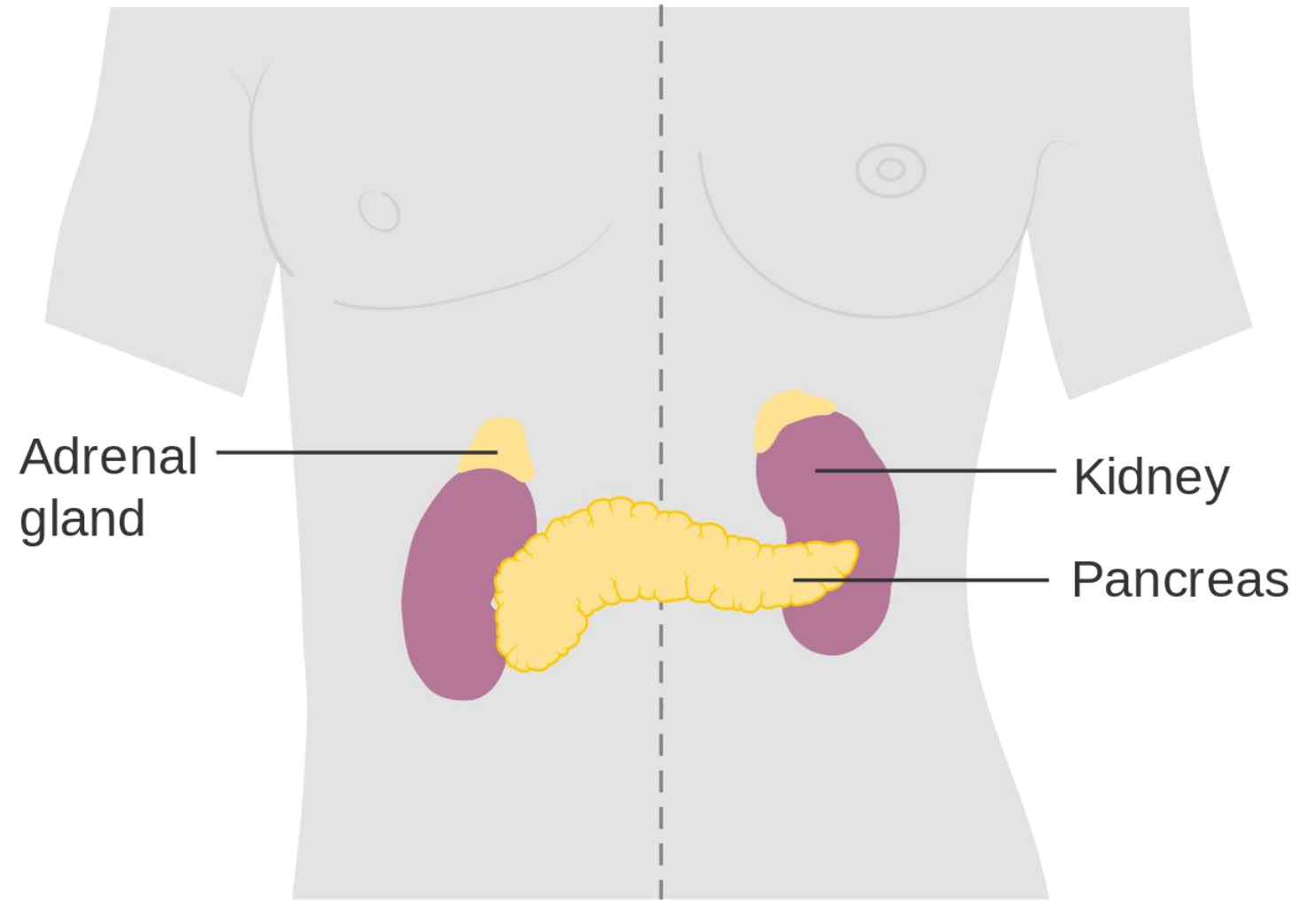
Increase rate of depression and suicide rate (up to 18%)

Apathy, sleep disturbances, personality change and hallucinations

Visual and verbal memory impairments

Paranoia inversely correlated with hormone levels

Adrenal Disorders



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Adrenal Disorders: Insufficiency

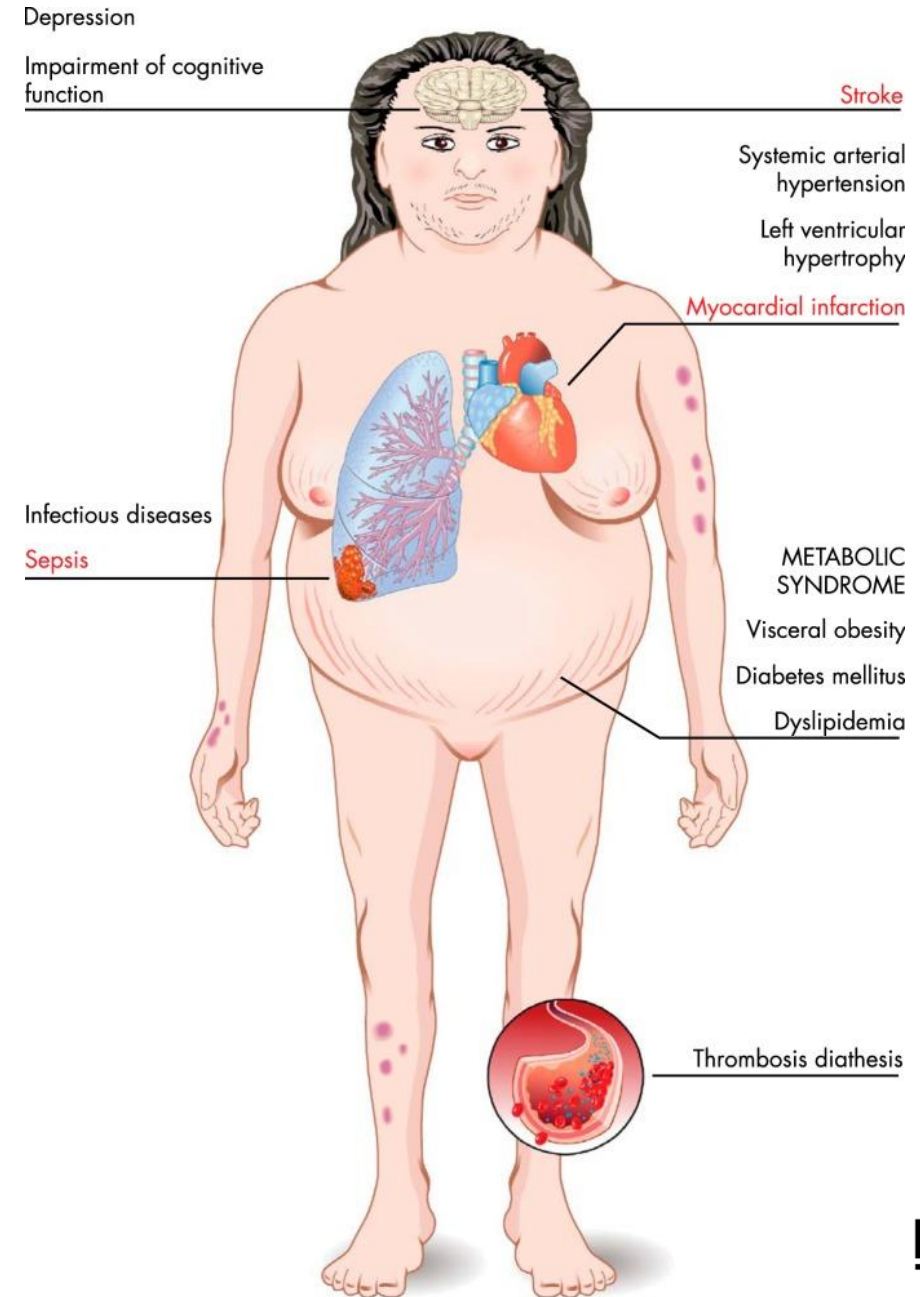


- Primary Insufficiency
 - Impairment of adrenal glands, **Addison disease**
 - Prevalence of 64-84%, most commonly mild mood fluctuations, motivation and behavior
 - Cognitive deficits less common and less studied and understood
 - Less common psychosis and delirium
 - Physical symptoms include fatigue, weight loss, abdominal pain.
 - Replacement with Hydrocortisone
- Secondary Insufficiency
 - Impairment of pituitary gland
- Tertiary Insufficiency
 - Hypothalamic disease and decrease in Corticotropin-releasing factor (CRF)

Adrenal Disorders: Hypercortisolism

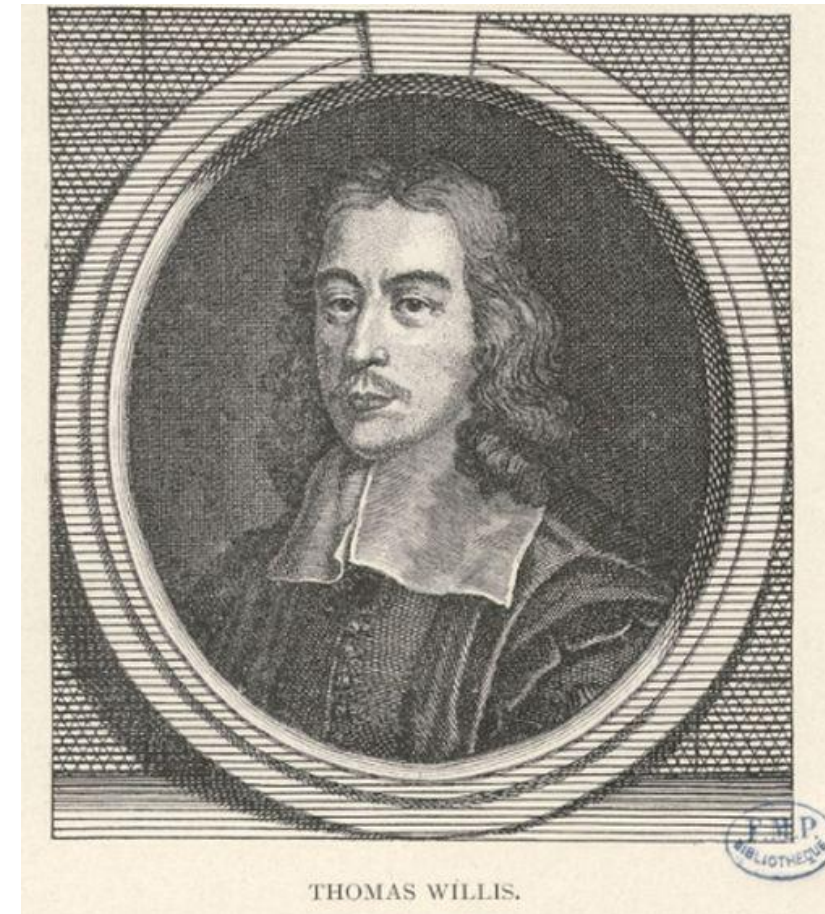
Cushing's Disease

- Major depression, present 50-80% across studies
- Higher cortisol in patients with depression
- Elderly, female, more severe clinical condition
- Generalized Anxiety Disorder 79% and Panic Disorder 50%
- Mood fluctuations, hypomania or mania 30%
- Multi-domain cognitive dysfunction: nonverbal, visual-ideational, visual memory and spatial-constructional; concentration, memory, reasoning and processing new information
- After control of hypercortisolism, prevalence of psychopathology was 54% (3mos), 36% (6mos) and 24% (12mos)



Diabetes and depression

- Thomas Willis recognized the connection between diabetes and depression in the 17th century.
- Stressful situations (“Sadness or long sorrow”).
- Chronic sadness
- Bidirectional link. Worse prognosis when occurring concurrently.
- Prevalence 11.3 % (ADA, 2019), 30% in older adults.



Case 2: 65 y/o F with MDD, new onset DM

- PMH: HTN, Obesity (BMI: 32).
- PPHx: MDD, moderate, episodic
- Course of illness: Good response to SSRI. Functional/employed.
- Dx of DM2 at age 62: worsening irritability, insomnia, anhedonia

Did you know?

In any 18-month period, 33% to 50% of people with diabetes have diabetes distress.

Did you know?

People with diabetes are 20% more likely to have anxiety at some point in their life than people without diabetes.

Did you know?

Only 25% to 50% of people with diabetes who have depression get diagnosed and treated.



- Diabetes Mellitus (DM) and Psychiatric Illness
 - Depression is **twice** more common in diabetics than general population
 - Comorbidity can affect motivation, compliance, quality of life, cost of care, end-organ, utilization of healthcare services (ED, hospitalizations)
 - Depression can lead to diabetes and vice versa
 - Health-related behaviors and psychological coping “diabetes specific distress”
 - Abnormalities HPA, sympathoadrenal systems and increased insulin-resistance, elevated HgA1C
 - Screening for depression and anxiety is important (PHQ-9, HADS-D, GAD-7)
 - Major challenge for medicine



- Similar treatment for depression and anxiety
 - SSRIs preferred versus TCAs (glycemic control, changes in appetite, carbohydrate cravings, weight gain, anticholinergic and cardiac effects)
 - Careful with use of benzodiazepines and beta-blockers, can mask hypoglycemia
 - Challenges, higher rate of suicidal ideas, overdose, cognitive dysfunction
 - CBT and problem-solving therapy
 - Collaborative care

Diabetes Mellitus and Cognition

- Faster decline in MMSE than non-diabetics for both type I and II DM, executive function, processing speeds, attention. Deficits can occur early in course of illness.
- Double the risk to develop vascular dementia (VD), Alzheimer's dementia (AD) or mixed dementia.
- Accumulation of advanced glycosylated end-products (AGEs) causes tissue damage and inflammation of cerebral vasculature.
- Diabetic autonomic neuropathy (DAN) is associated to poor control of **hypertension** and increases the risk for cerebrovascular accidents (CVA).
- Hyperinsulinemia leading to microvascular damage and interference of amyloid precursor protein metabolism leading to beta-amyloid deposits.

Hypoglycemia

Neurogenic / Autonomic (hyperadrenergic)

- Tachycardia
- Diaphoresis
- Tremors
- Weakness
- Hunger
- Irritability
- Panic attack-like episodes

Neuroglycopenic (<40 mg/dL, low glucose to CNS)

- Faintness
- Headaches
- Blurry vision
- Lethargy
- Confusion
- Dizziness
- Weakness
- Incoordination
- Behavioral changes
- Reversible focal neurological findings
- Seizures
- Coma

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What We Covered: Key Takeaways

- **Thyroid:** hypothyroidism may mimic depression, hyperthyroidism may mimic anxiety and psychosis; check TSH in atypical, refractory and older patients
- **Parathyroid:** check calcium — symptom severity tracks the calcium level, from irritability to psychosis
- **Pituitary:** adenomas produce varied presentations; apathy may be the only feature
- **Adrenal:** insufficiency alters mood and motivation; hypercortisolism brings depression, anxiety and multi-domain cognitive dysfunction
- **Diabetes:** bidirectional with depression, worse prognosis together, and accelerated cognitive decline

Conclusions/Recommendations

- **Treat both sides of the endocrine/mental health loop:** treating one side alone leaves the cycle intact.
- **Discuss** with patients how endocrine function affect the brain.
- Neuropsychiatric symptoms often precede or accompany the physical signs of endocrine disorders.
- **Watch psychotropic–endocrine interactions:**
 - Lithium – hypercalcemia, PTH elevation (chronic use)
 - Antipsychotics – prolactin elevation from D2 blockade
 - Diabetes – prefer SSRIs over TCAs
 - Beta-blockers and benzodiazepines can mask hypoglycemia
- Multidisciplinary care is essential.
- Counsel on nutrition, exercise, and smoking cessation — they shape both endocrine and brain health.

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Questions?

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