Endocrine and Metabolic Disorders: A Medical Psychiatry Focus

Catherine Gonzalez, M.D.

Associate Chief, Division of Geriatric Psychiatry and Aging | MGB AMC Psychiatry
Medical Director of Faculty, Trainee & Employee Mental Health | Brigham & Women's Hospital
Assistant Professor of Psychiatry | Harvard Medical School
cgonzalez7@bwh.harvard.edu

New:

- Consider li orotate slide/dementia? GLP-1?
- Change Metabolic conditions to 3-4 most common

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

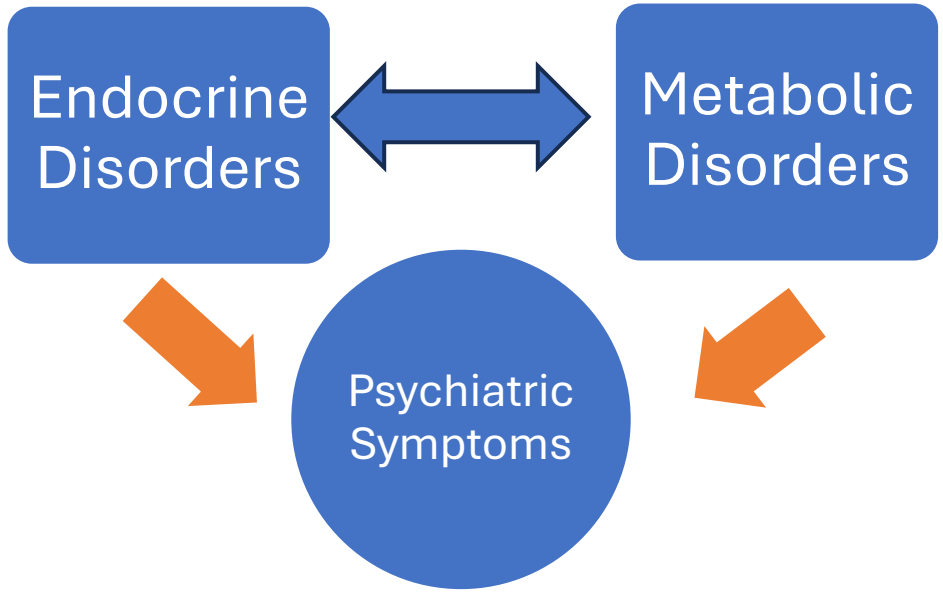
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

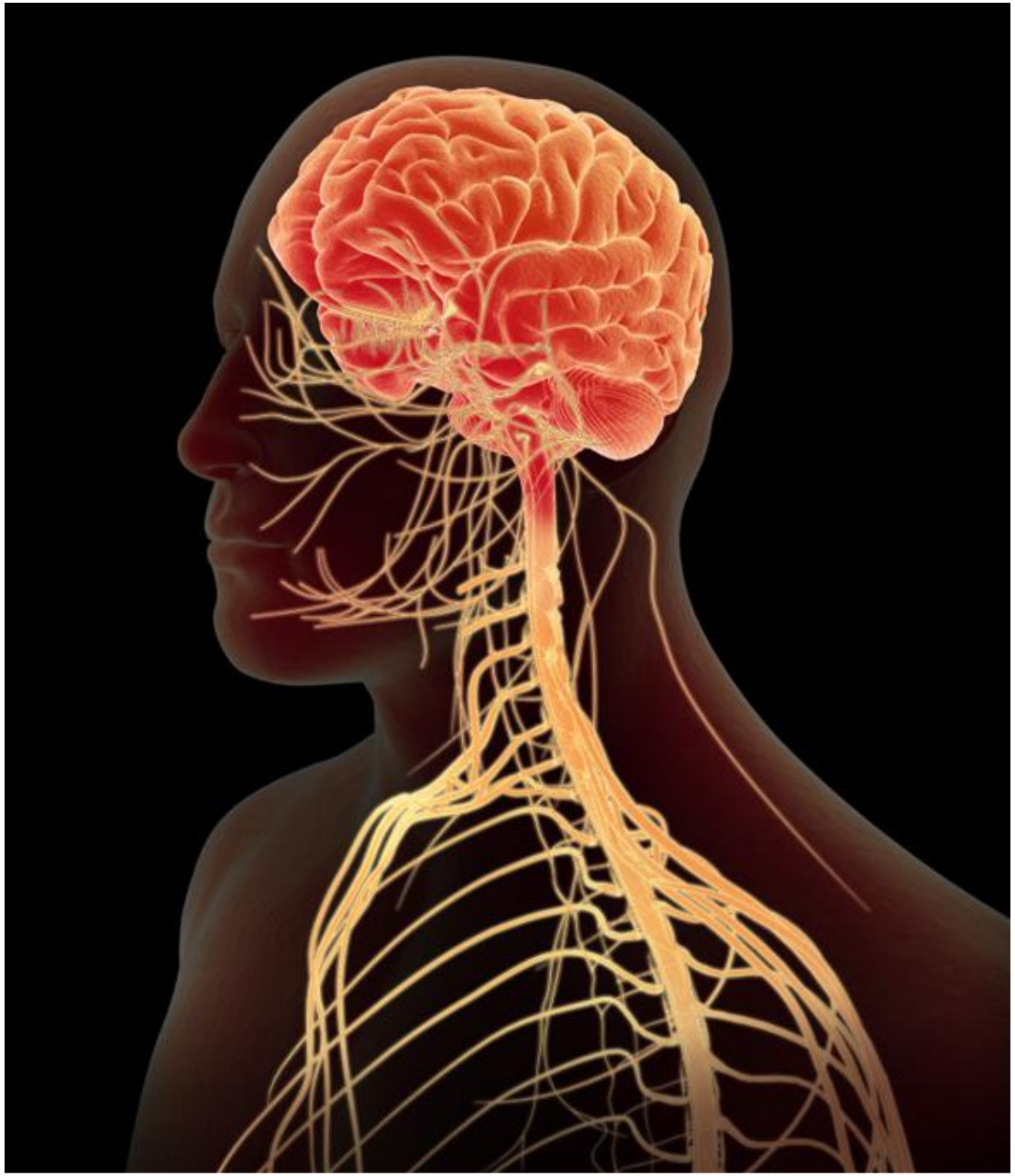
Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose

Objectives:

1)To understand the bidirectional relationship among endocrine & metabolic conditions and psychiatric symptoms.

2) To review most common Endocrine and Metabolic disorders that can lead to psychiatric symptoms.





Topics:

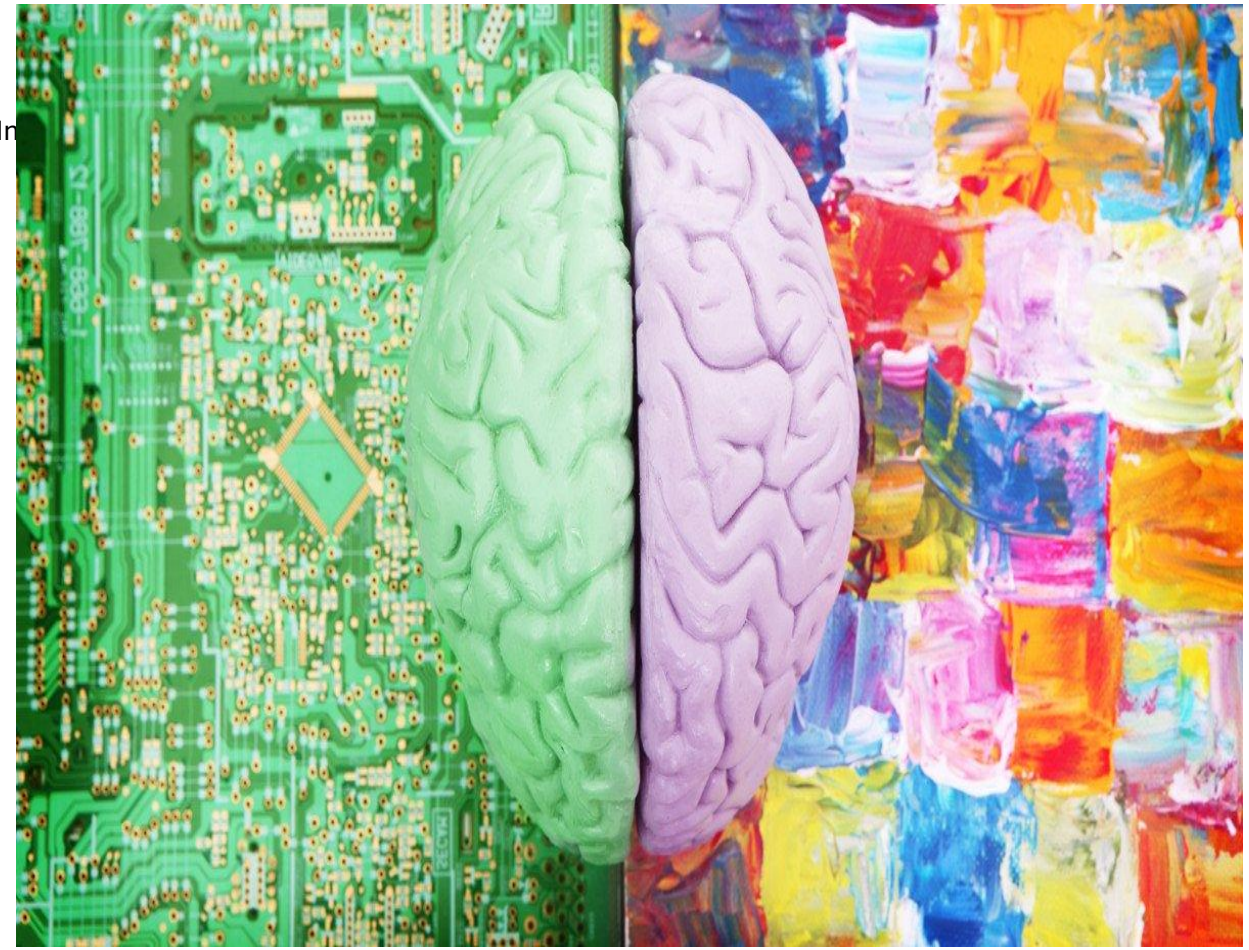
1. Endocrine Disorders
- Thyroid
- Parathyroid
- Pituitary
- Adrenals

2. Diabetes
- DM and depression
- DM and cognition
- Hypoglycemia

3. Metabolic Disorders
- Metabolic Syndrome
- Mitochondrial Disorders
- Urea Cycle Disorders
- Acute Intermittent Porphyria
- Wilson's disease

Potential Mechanisms:

(In



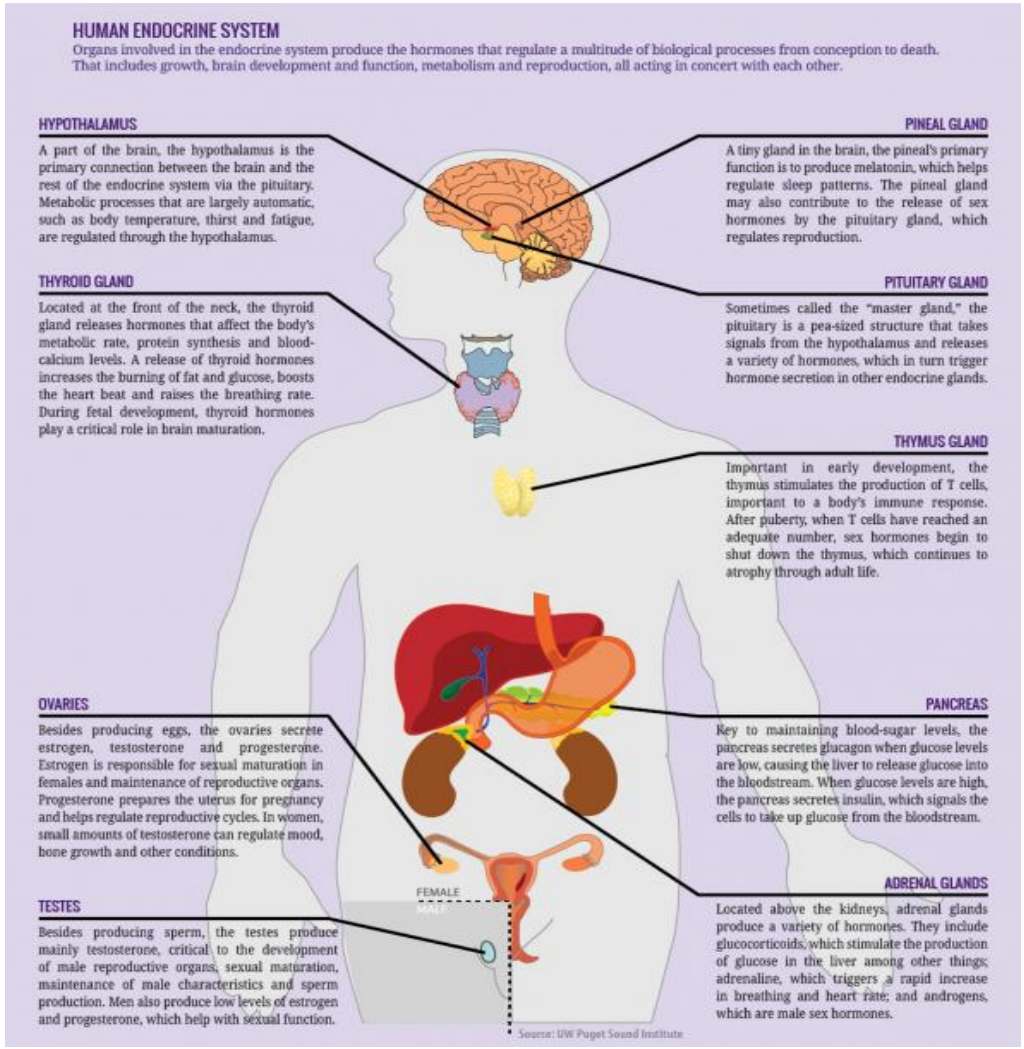
Pathophysiologic process

- Neuronal metabolism
- Synaptic transmission
- Direct inflammation of brain tissue

Psychological reaction to the illness

- Affects function and Quality of life
- Leads to further impacts in brain processes.

Endocrine Disorders:

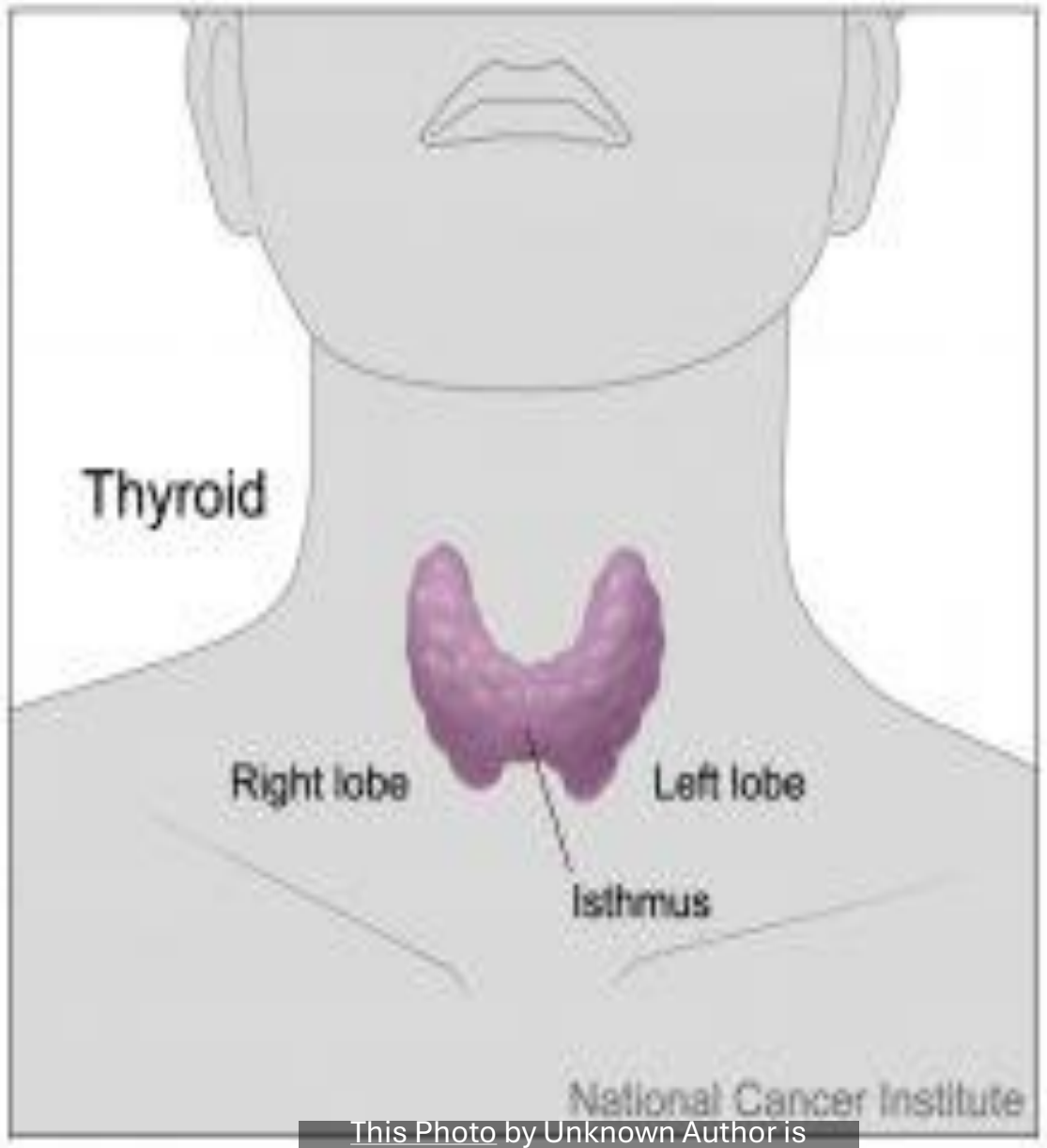


- Thyroid
- Parathyroid
- Pituitary
- Adrenals

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

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Disorders of the Thyroid



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 Thyroid

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

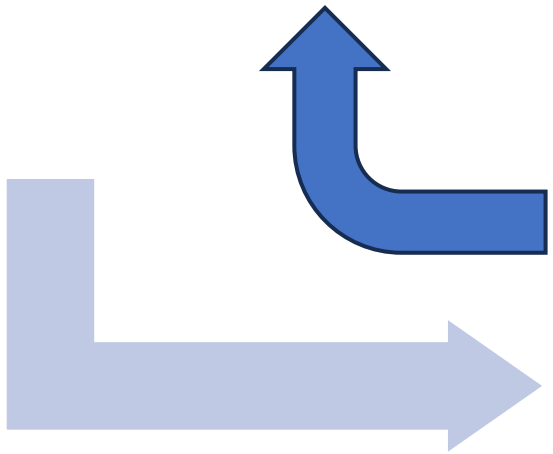
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Hyperthyroidism

Hyperthyroidism (Thyrotoxicosis)

Neuropsychiatric and Cognitive Symptoms

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



Physical Symptoms

- 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

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

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

- 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 nonsupressed and 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 2weeks-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.*

Management of Subclinical Hyperthyroidism, Int J Endocrinol Metab 2012

Disorders of Thyroid

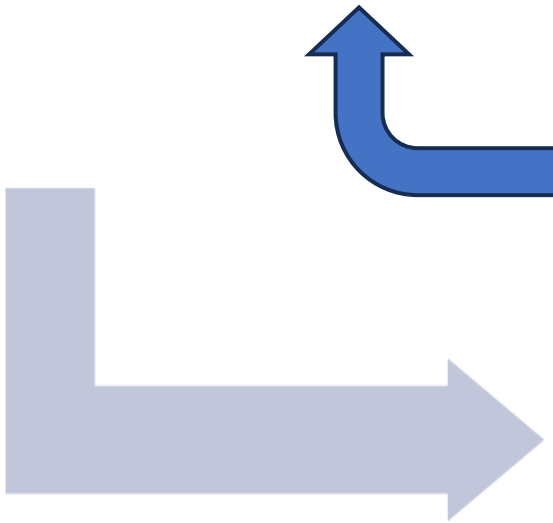
Hypothyroidism (Myxedema)

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

Hypothyroidism (Myxedema)

Neuropsychiatric and Cognitive Symptoms

- 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 Symptoms

- 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 thyroid gland itself.

- Secondary or tertiary hypothyroidism
  - TSH below normal/Nml with low fT4, pituitary or hypothalamic dysfunction

- *Subclinical hypothyroidism: ↑serum TSH, with normal levels of FT4.*
  - *Increase risk for atherosclerosis, cardiac events.*
  - *Increased risk of cognitive impairment, fatigue, low mood.*
  - *Meta-analysis, up to 50% 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*

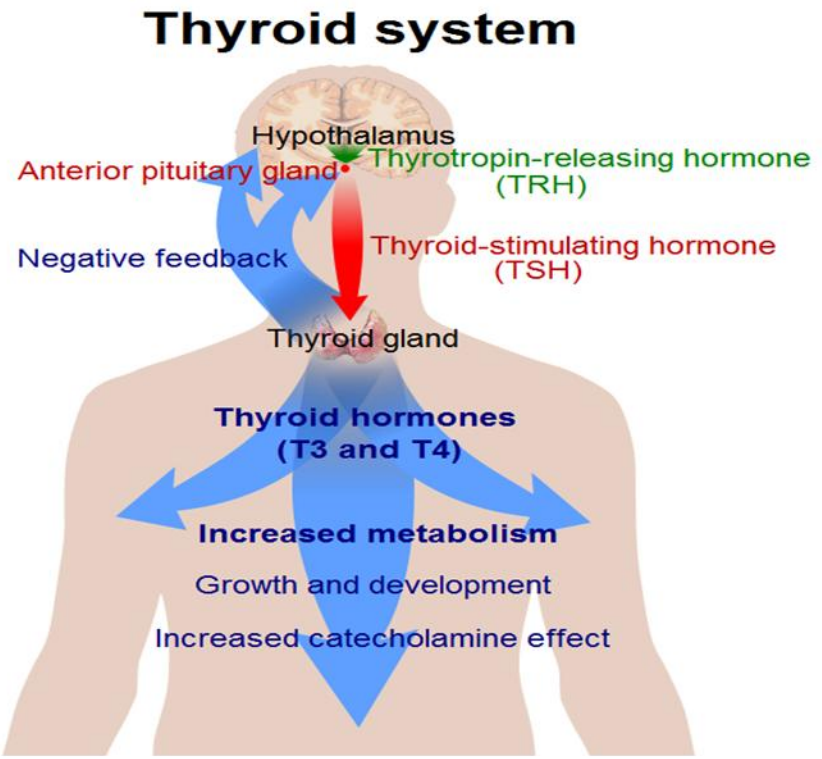
Front. Endocrinol., 2019

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

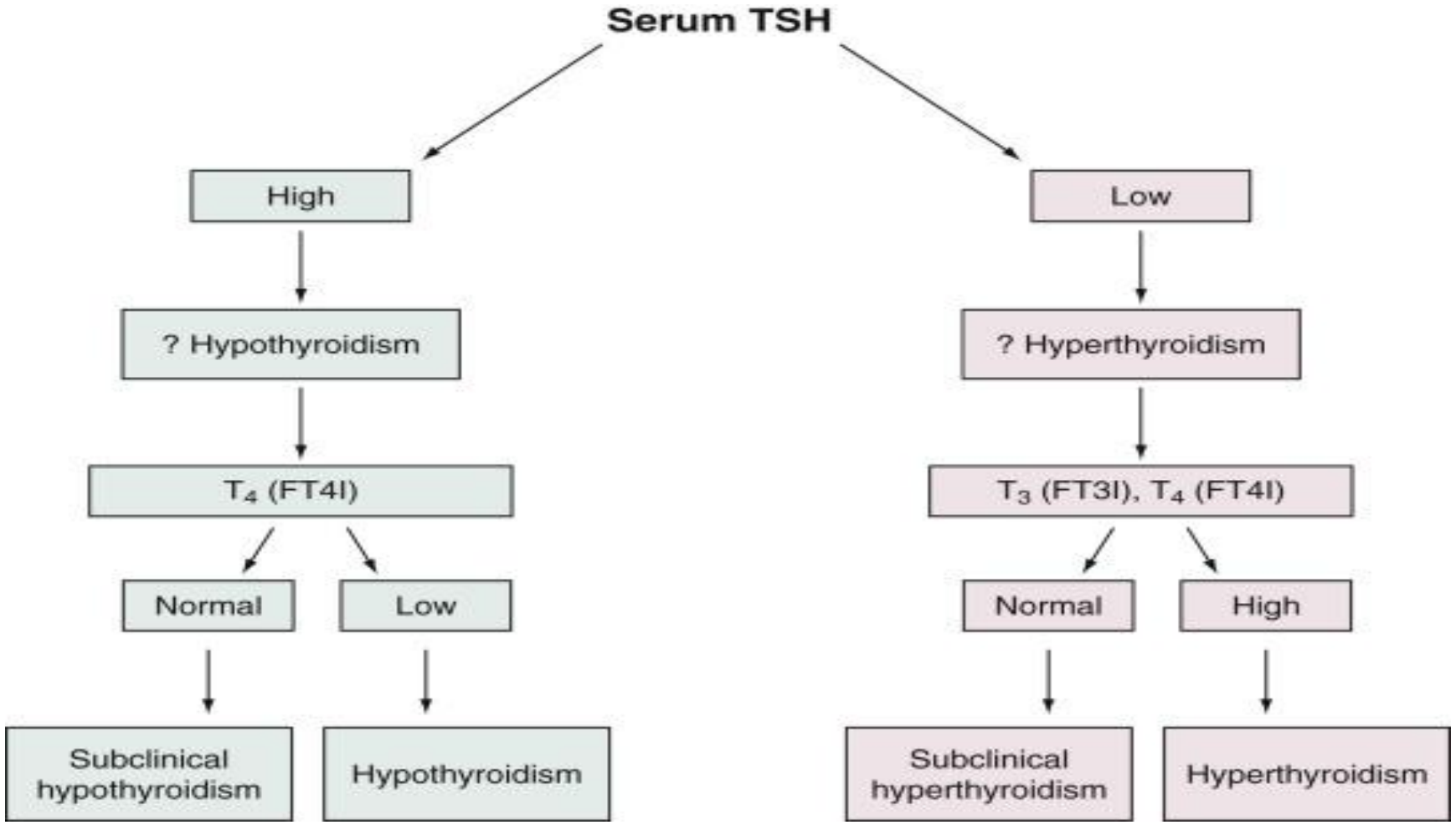
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Laboratory tests

- Thyroid stimulant 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 process of de-iodination.
- Combination is highly sensitive and specific to detect deficiency or excess



Screening for thyroid disorders



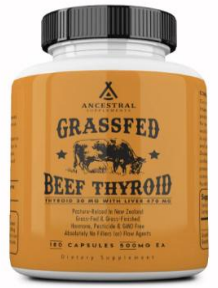
Screening and Treatment of Subclinical Hypothyroidism or Hyperthyroidism

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

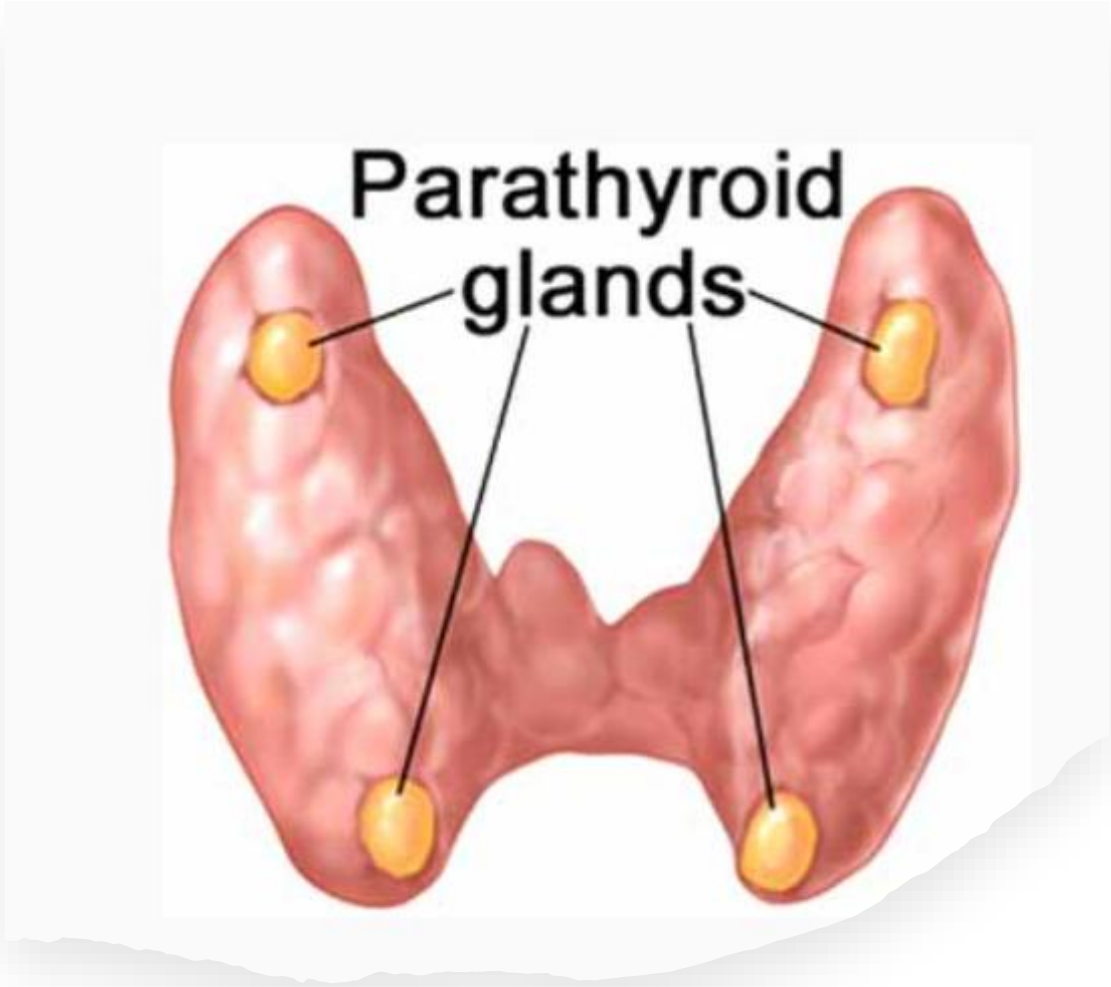
Augmentation with Thyroid Hormone

- 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, arrythmias, hyperthyroidism Sx.
- Efficacy is independent of baseline TSH.
- Heard of Desiccated Thyroid? Derived from bovine/porcine thyroid gland (T3/T4→1:4).
- https://www.fda.gov/drugs/enforcement-activities-fda/fdas-actions-addr unapproved-thyroid-medications



Am J Psychiatry. Hormonal Tx for MDD 2020

Parathyroid Glands Disorders



https://thyroidendocrine.com/parat

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

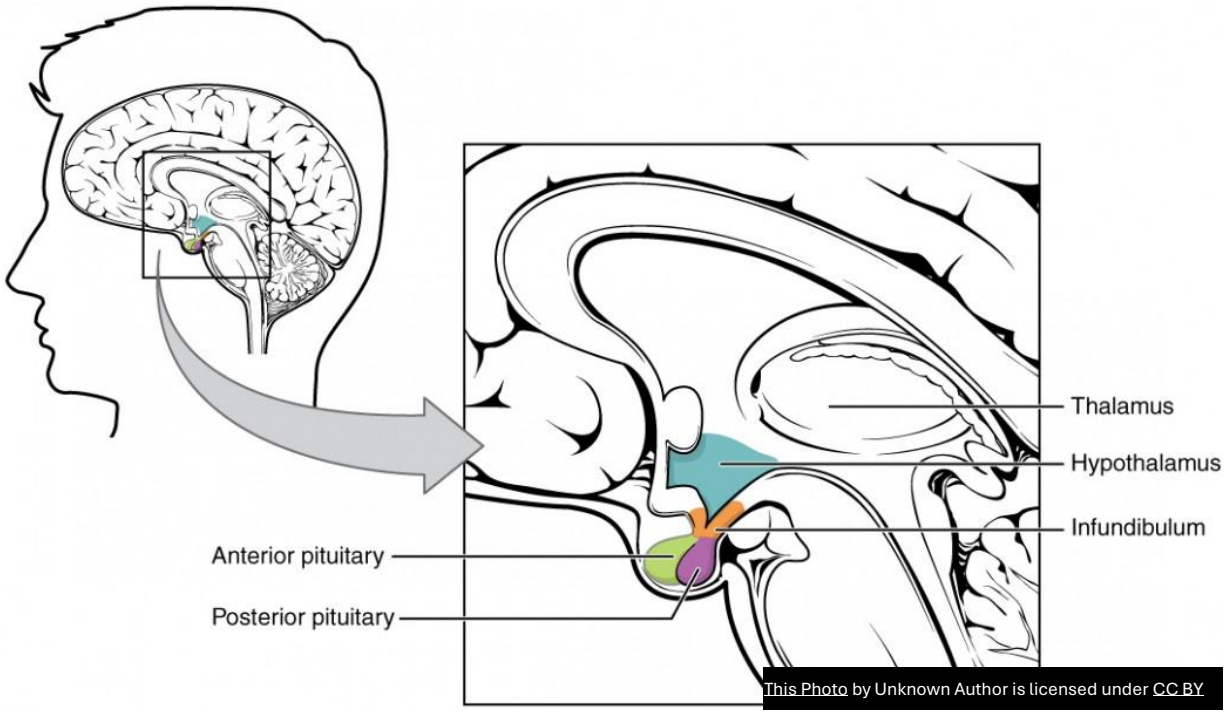
Serdenes, R., Lewis, M., & Chandrasekhara, S. (2021). A Clinical Review of the Psychiatric Sequelae of Primary Hyperparathyroidism. *Cureus*, *13*(10), e19078. https://doi.org/10.7759/cureus.19078

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

Disorders of Pituitary Function



- 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

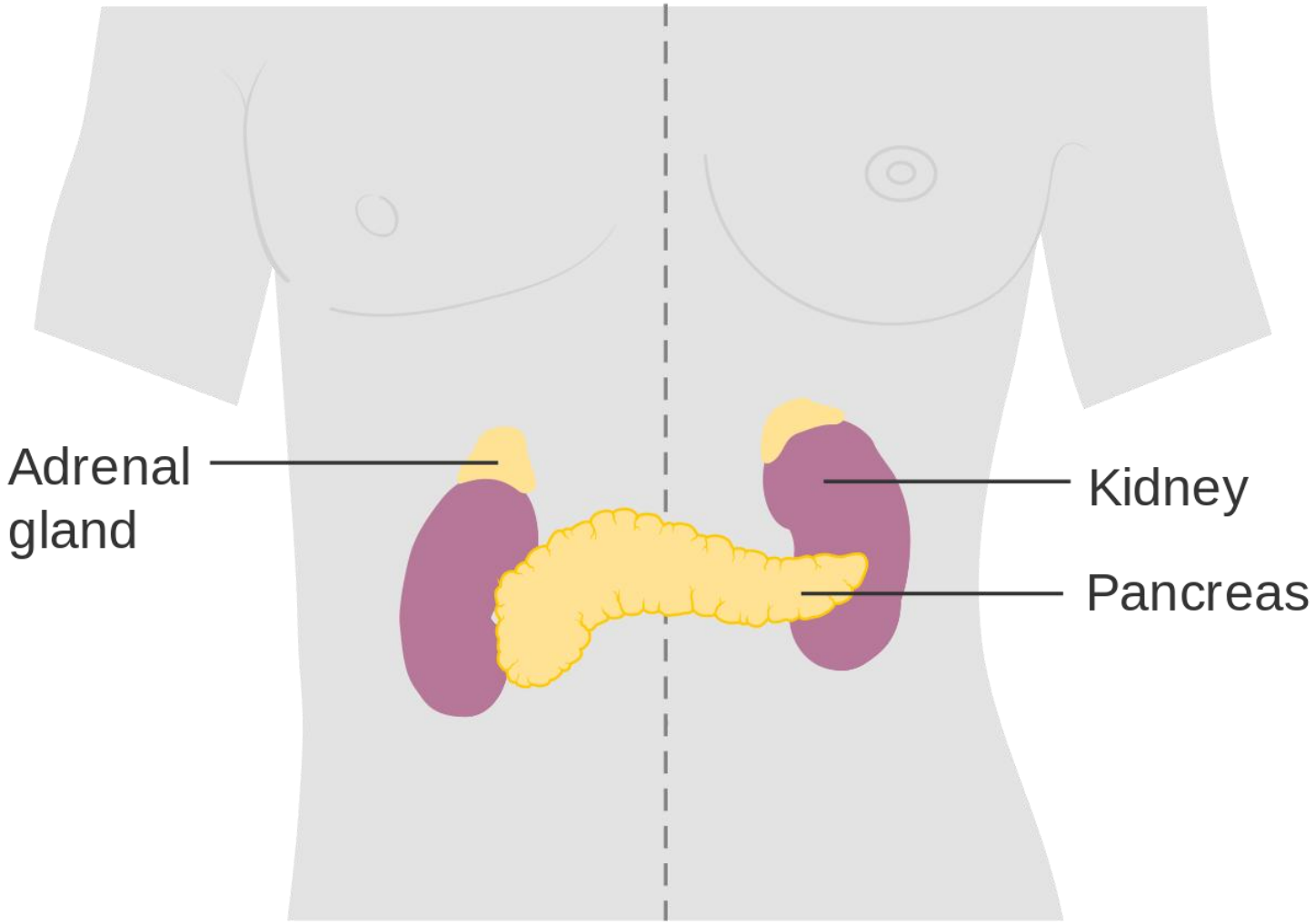
Disorders of Pituitary Function: Hypopituitarism

- 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

Lithium and hyperparathyroidism

- Chronic treatment
- “Unmasking” native hyperparathyroidism
- Causal hyperplasia of gland
- Promote growth adenomas
- Direct stimulation of PTH
- Hypocalciuria related to renal dysfunction
- Interference with calcium-mediated transmembrane signals

Adrenal Disorders



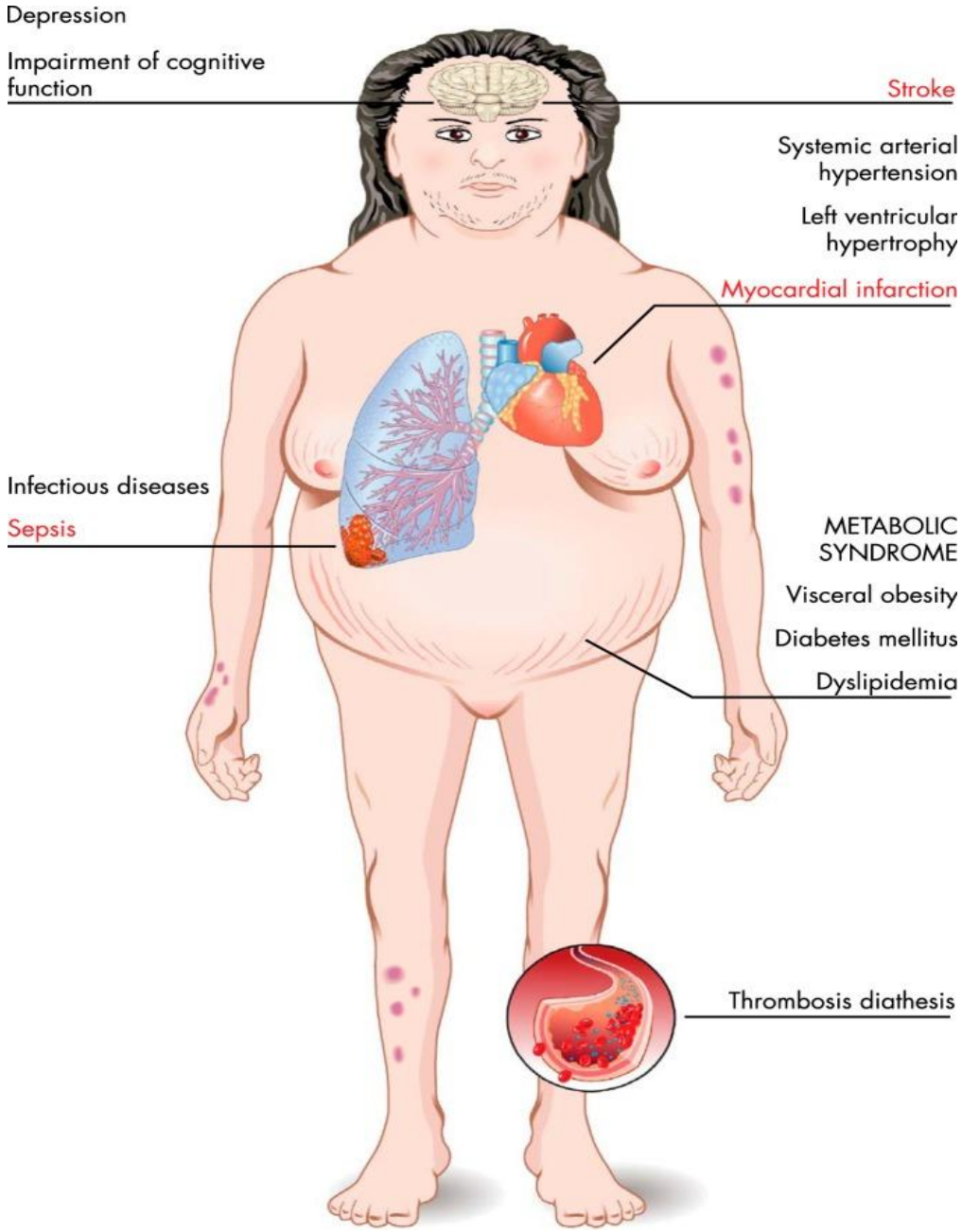
Adrenal Disorders: Insufficiency

- 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)



Pivonello R, De Leo M, Cozzolino A, Colao A. The Treatment of Cushing's Disease. *Endocr Rev*. 2015;36(4):385-486. doi:10.1210/er.2013-1048

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 @ age 62.→ worsening in irritability/insomnia/anhedonia

Did you know?

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

CDC: Diabetes and Mental Health

Disorders of Glucose Metabolism: DM

- 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

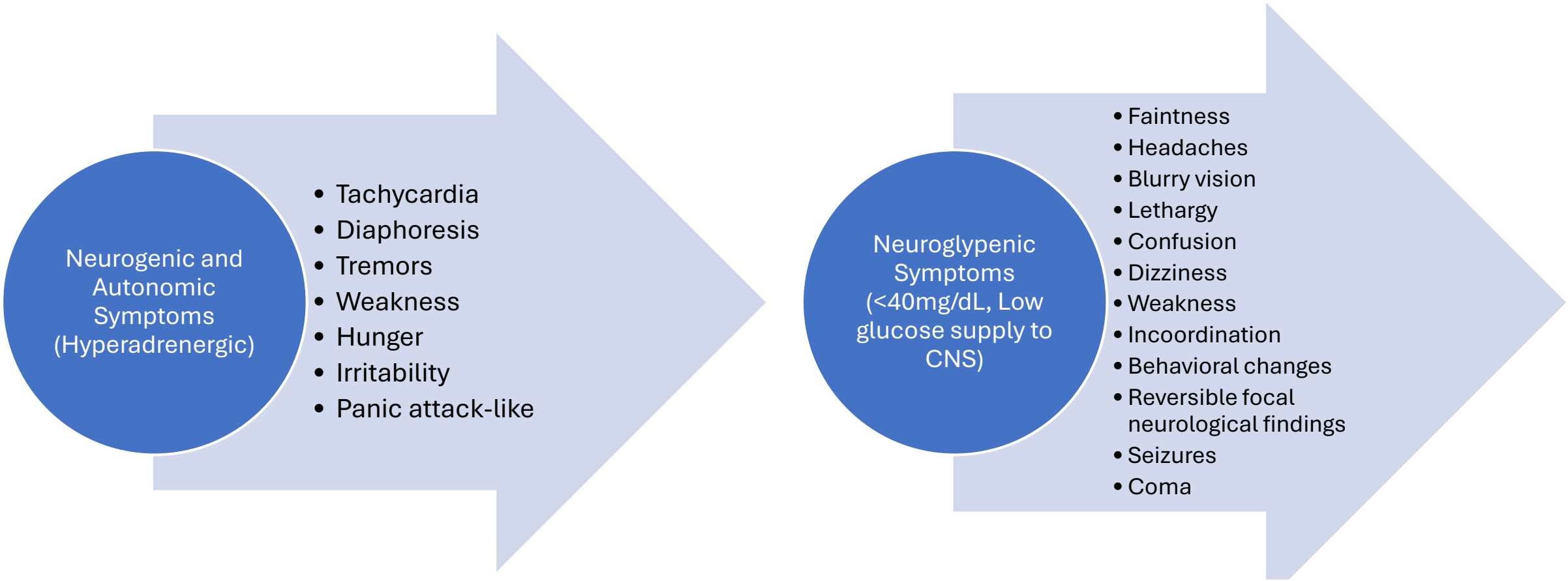
Disorders of Glucose Metabolism: DM (cont.)

- 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



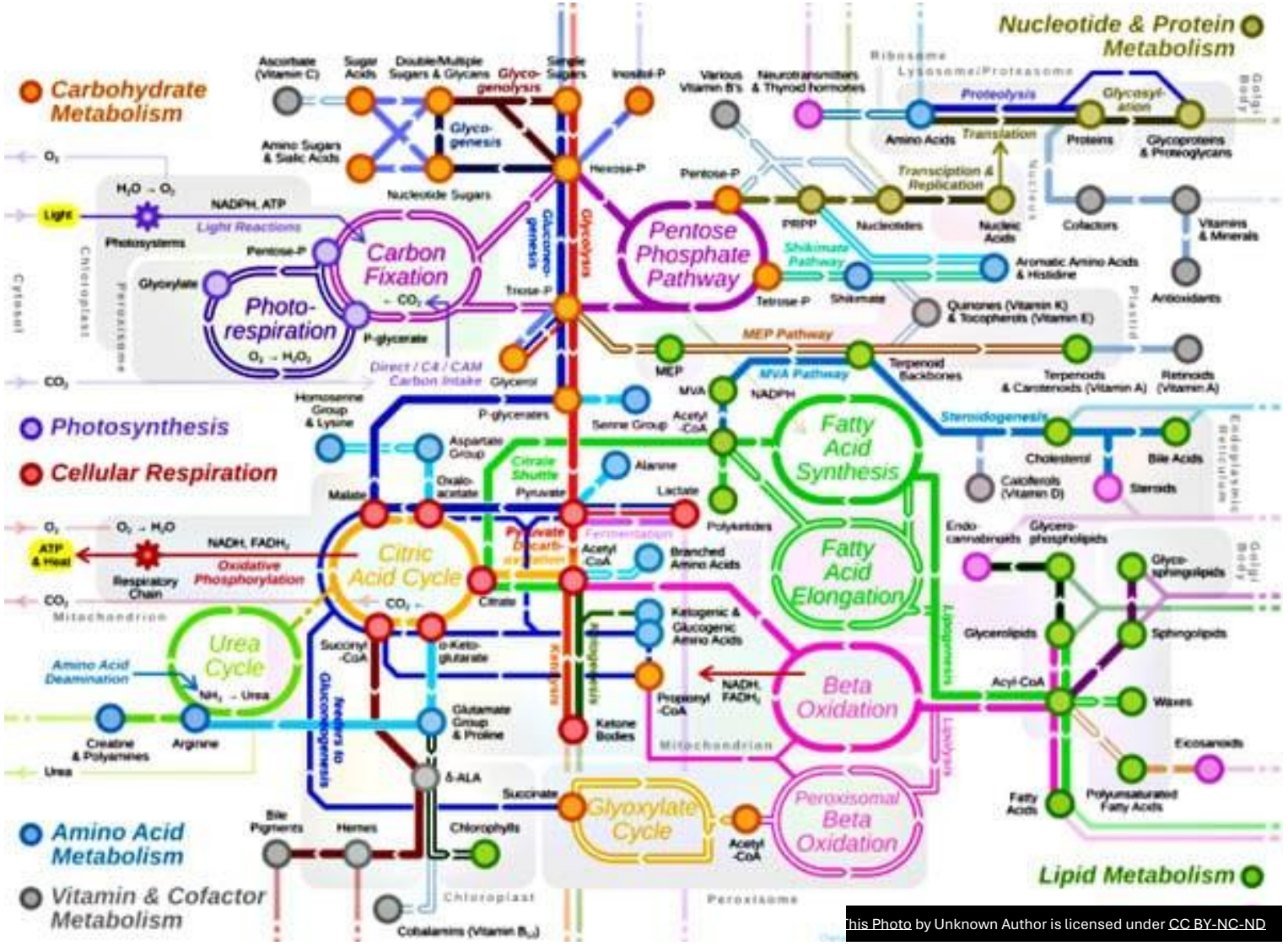
Hypoglycemia

- Chronic hypoglycemia, slow thinking, depression, phobia of hypoglycemia and caregiver burden, young and elderly more vulnerable
- Associated with a spike in epinephrine.
- Careful use of beta-blockers

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

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Metabolic Disorders:



Case 3: 65 y/o M with Schizophrenia who presents for an evaluation.

- PMHx: HTN, Hyperlipidemia, Obesity, DM.
- PPHx: Chronic Schizophrenia, improved positive symptoms on atypical antipsychotic (Risperidone).
- Interim course: has self-decreased his dose due to weight gain concerns. Worsening depression, re-emergence of paranoia. Now with limited activity, difficulty leaving his home or going to medical appointments.

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

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Metabolic Syndrome:

Table 1

Diagnostic criteria for metabolic syndrome[a]

Criterion	Clinical value
Abdominal obesity	Waist circumference >40 inches (men) or >35 inches (women)
Hypertriglyceridemia	≥150 mg/dL
Low HDL cholesterol	<40 mg/dL in men <50 mg/dL in women
Hypertension	Blood pressure ≥130/85 mm Hg
High fasting glucose	≥110 mg/dL

[a]Diagnosis of metabolic syndrome is based on the presence of any 3 of the above 5 features

HDL: high-density lipoprotein

Source: Reference 4

Table 2

Most common causes of death in individuals with significant mental illness

Cardiovascular disease	33.9%
Cancer	21%
Pulmonary disease	13.5%
Suicide, homicide, and accidents	5.4%[a]

[a]No statistically significant difference compared with matched control group

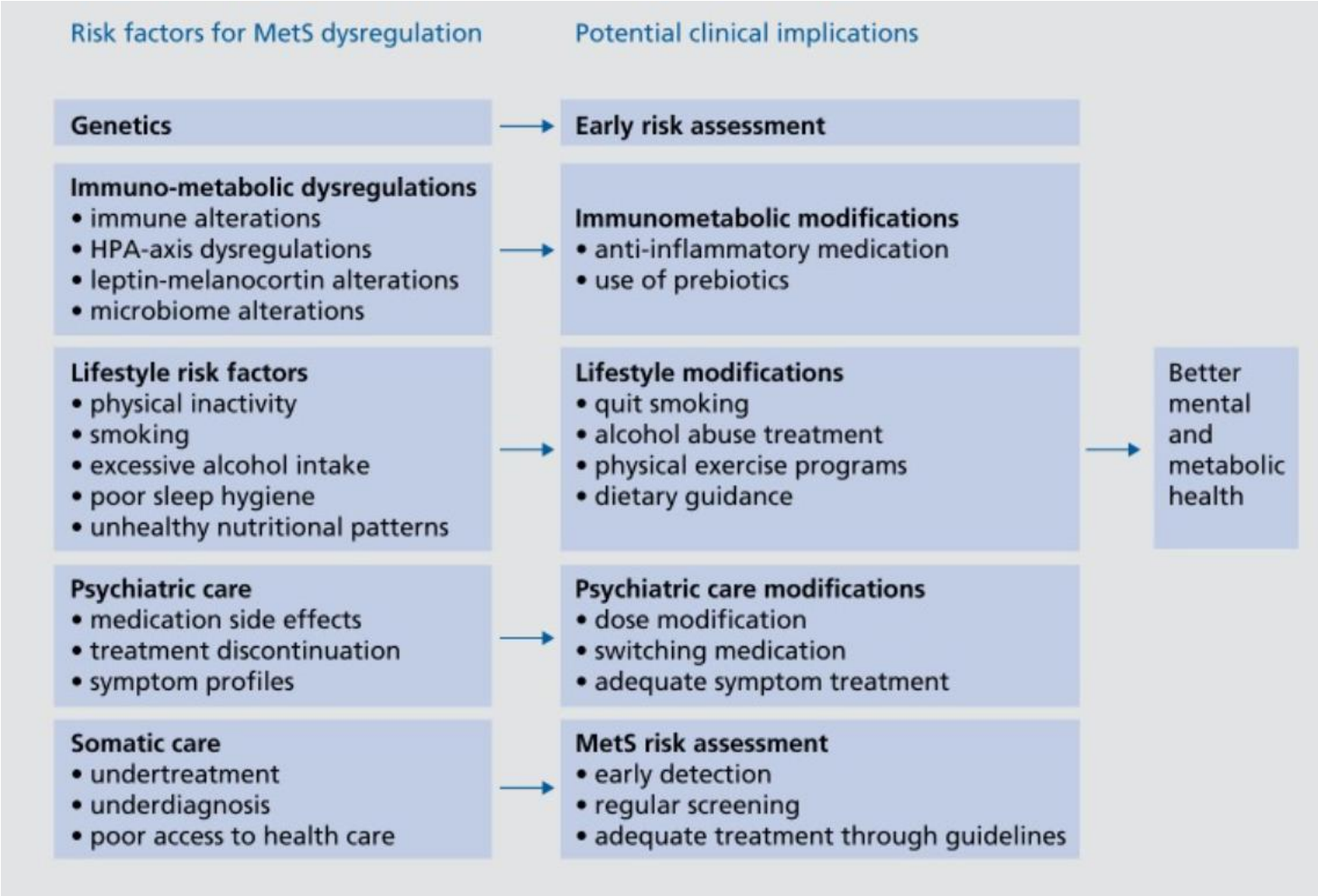
Source: Reference 5

Current Psychiatry "Managing Metabolic Syndrome in Patients with Schizophrenia"

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

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Metabolic Syndrome:



Metabolic syndrome in psychiatric patients - Penninx and Lange, 2018

Hereditary Metabolic Disorders (HMD's)/ Inborn Errors of Metabolism (IEM's)

- Rare (1:800-1:1000) but important cause of psychiatric symptoms in adolescents/young adults.
- Metabolic screening in psychosis: 1/20 patients could have a underlying untreated metabolic disorder.
- "Late onset HMD" might present with isolated psychiatric symptoms before physical symptoms appear.
- For some disorders: treatment is available. Treating early (when psychiatric symptoms are present) would have best efficacy.

- Nikita van de Burgt, Willem van Doesum, Mirjam Grevink, Stephanie van Niele, Tom de Koning, Nicole Leibold, Pilar Martinez-Martinez, Therese van Amelsvoort, Danielle Cath,
- Psychiatric manifestations of inborn errors of metabolism: A systematic review, Neuroscience & Biobehavioral Reviews, Volume 144, 2023, 104970, ISSN 0149-7634, https://doi.org/10.1016/j.neubiorev.2022.10

Psychiatric manifestations of inborn errors of metabolism: A systematic review

Nikita van de Burgt [a,*], Willem van Doesum [b,c], Mirjam Grevink [c], Stephanie van Niele [c], Tom de Koning [c,d,e], Nicole Leibold [a], Pilar Martinez-Martinez [a], Therese van Amelsvoort [a], Danielle Cath [b,c]

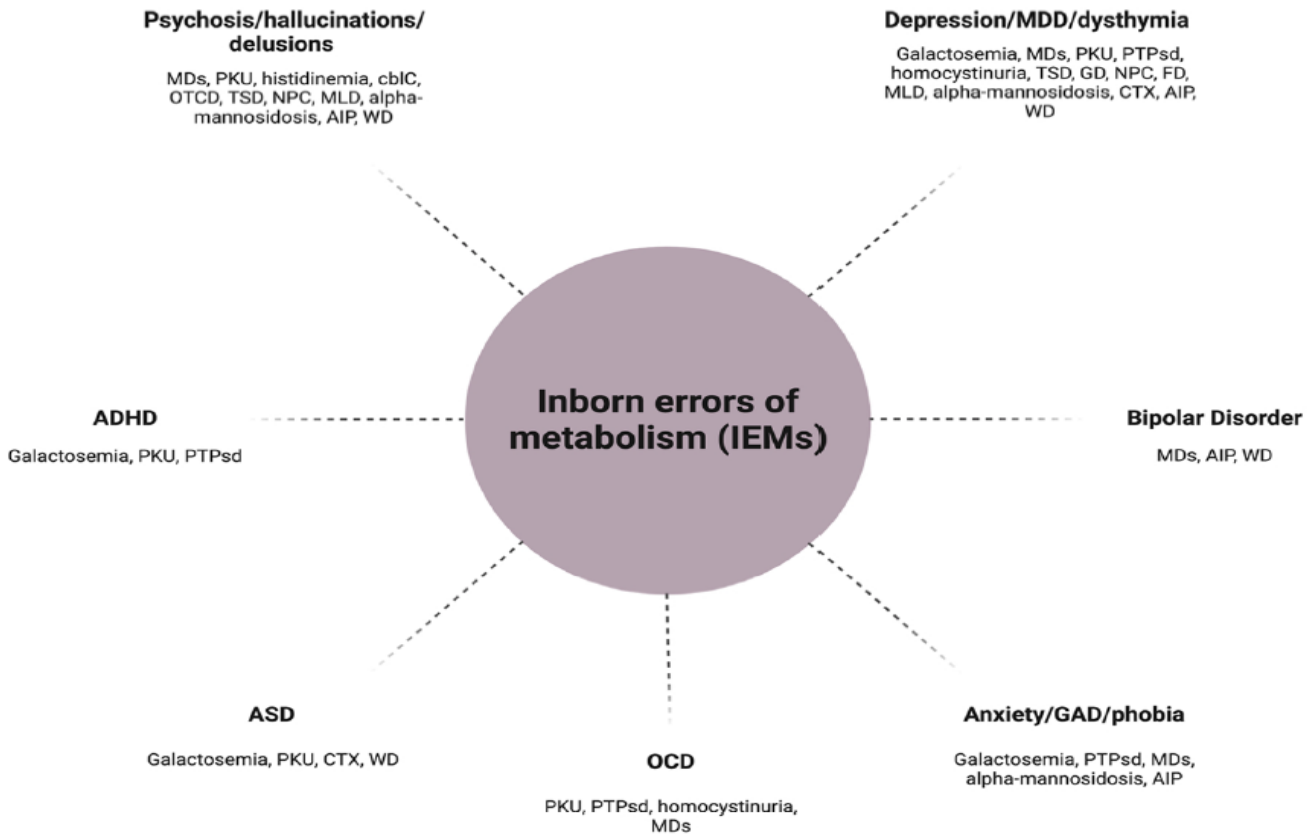
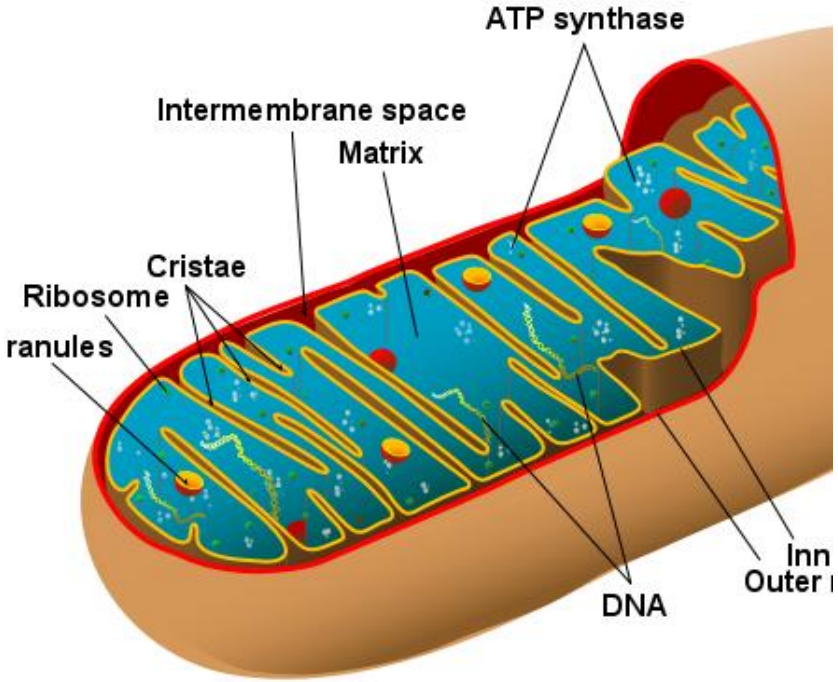


Fig. 2. Overview of psychiatric manifestations of inborn errors of metabolism. MDs = mitochondrial disorders, PKU = phenylketonuria, cblC = cobalamin C disorder, OTCD = ornithine transcarbamylase deficiency, PTPsd = 6-pyruvoyl-tetrahydropterin synthase deficiecy, TSD = tay-sachs disease, GD = Gaucher disease, NPC = Niemann-Pick disease type C, FD = Fabry disease, MLD = metachromatic leukodystrophy, CTX = cerebrotendinous xanthomatosis, AIP = acute intermittent porphyria, WD = wilson's disease, MDD = major depressive disorder, GAD = generalized anxiety disorder, OCD = obsessive compulsive disorder, ASD = autism spectrum disorder, AHDH = attention deficit hyperactivity disorder.

Inherited Mitochondrial Disorders

- Mutations in mtDNA: MELAS, MERRF, NARP.
- Neuropsychiatric manifestations: psychosis, anxiety, depression, intellectual disability.
- Physical symptoms: chronic fatigue, muscle weakness, exercise intolerance.
- Conflicting findings re: severity of MD with levels of depression/anxiety/psychiatric symptoms.



IEM: Urea Cycle Disorders

Urea Cycle→ Liver metabolic pathway: eliminates excess nitrogen via detoxification of ammonia into urea.

Group of multiple disorders, abnormalities of blood amino acids, deficiencies of 6 enzymes or 2 transporters.

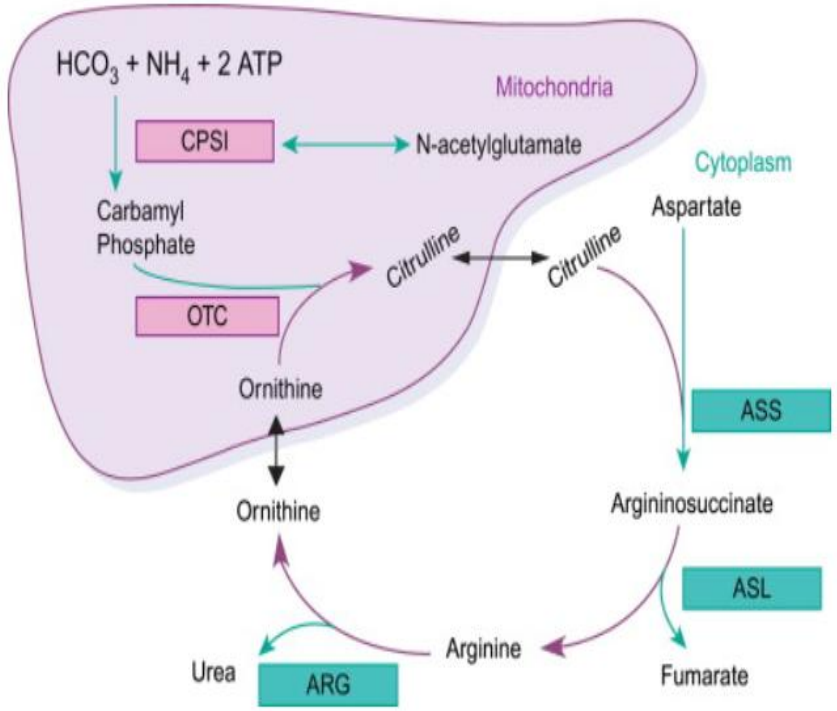
Can occur at ANY age, most in neonatal/young children but some late onset.

Increase in ammonia: changes in blood flow, metabolism, toxicity to brain.

Most common symptoms: confusion, psychosis, behavioral disorders, hallucinations.

Can be accompanied by headaches/GI symptoms

Potential protein intolerance/change in diet.



IEM: Acute intermittent porphyria

Autosomal dominant, variable penetrance

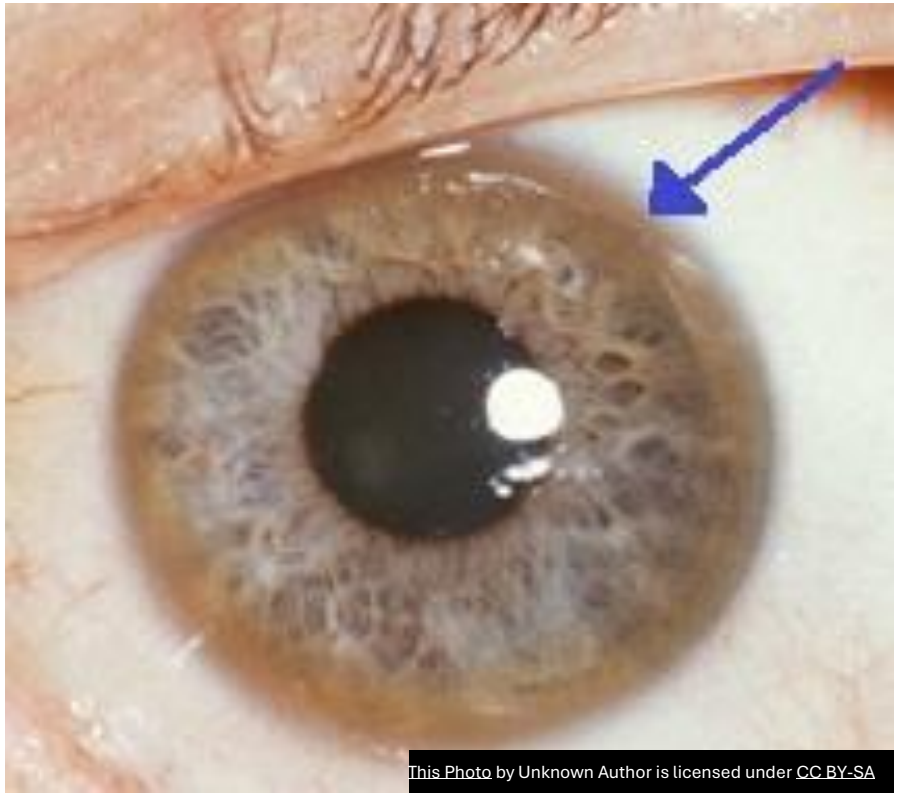
Disruption of heme biosynthesis: accumulation of pophyrins

“Attacks”: anxiety, insomnia, irritability, hypervigilance, psychosis, pain.

Often cyclical. Strong association with psychiatric disorders

IEM: Wilson's Disease

- Autosomal Recessive inheritance (chr 13), role in copper metabolism.
- Toxic build up of copper in liver and CNS. Can be asymptomatic until it presents in childhood up to ages late 50-60's.
- Psychiatric symptoms: irritability, aggression, obsessions, depression, tremors, rigidity, akinesia.



Red flags for underlying HMD's

Table 2
Red flags for an underlying IEM within the psychiatric field.

Red flags	Examples
Atypical psychotic symptoms	Visual hallucinations, confusion, acute onset, treatment resistance, unusual or severe side effects of a psychotropic drug
Atypical depression with psychotic symptoms	Visual hallucinations, confusion, acute onset, treatment resistance, unusual or severe side effects of a psychotropic drug
Strong and/or progressive cognitive decline	
Motor symptoms	Tremor, involuntary movements, involuntary muscle contractions or spasms
Intellectual disability	
Gastrointestinal and abdominal symptoms	Vomiting, diarrhea, (acute) abdominal pain
Exercise intolerance	Unusual or severe muscle cramps, fatigue and/or tenderness, nausea and/or vomiting after exercise and rapid loss of breath and/or insufficient heart rate during exercise
Other	Vertical supranuclear gaze palsy, Kaiser Fleischer rings

Conclusions/Recommendations

- Discuss with patient about the interplay of endocrine and metabolic functions and their impact on brain function
- Communicate to patients the importance and impact of nutrition, regular exercise and smoking cessation on those systems, brain and health in general
- Atypical symptoms/cases: +screen, potentially **refer** to specialist.
- Screening in ambulatory by using:
  - Depression – PHQ-2
  - Anxiety – GAD-2
  - Bipolar disorder – MDQ
  - Schizophrenia – History and consider co-managing with internal medicine due to risk and potential medication side effects
  - Cognitive deficit – Mini-Cog, MMSE, MOCA

References

- Anglin RE, Rosebush PI, Mazurek MF. The neuropsychiatric profile of Addison's disease: revisiting a forgotten phenomenon. J Neuropsychiatry Clin Neurosci. 2006 Fall;18(4):450-9. doi: 10.1176/jnp.2006.18.4.450. PMID: 17135373.
- Conner SH, Solomon SS (2017) Psychiatric Manifestations of Endocrine Disorders. J Hum Endocrinol 1: 007.
- Cusano NE, Bilezikian JP. Signs and Symptoms of Hypoparathyroidism. Endocrinol Metab Clin North Am. 2018 Dec;47(4):759-770. doi: 10.1016/j.ecl.2018.07.001. PMID: 30390811.
- Habib S, Sangaraju SL, Yepez D, Grandes XA, Talanki Manjunatha R. The Nexus Between Diabetes and Depression: A Narrative Review. Cureus. 2022 Jun 2;14(6):e25611. doi: 10.7759/cureus.25611. PMID: 35784974; PMCID: PMC9249007.
- Salvador, J., Gutierrez, G., Llavero, M., Gargallo, J., Escalada, J., López, J. (2019). Endocrine Disorders and Psychiatric Manifestations. In: Portincasa, P., Frühbeck, G., Nathoe, H.M. (eds) Endocrinology and Systemic Diseases. Endocrinology. Springer, Cham. https://doi.org/10.1007/978-3-319-66362-3_12-1
- van de Burgt N, van Doesum W, Grevink M, van Niele S, de Koning T, Leibold N, Martinez-Martinez P, van Amelsvoort T, Cath D. Psychiatric manifestations of inborn errors of metabolism: A systematic review. Neurosci Biobehav Rev. 2023 Jan;144:104970. doi: 10.1016/j.neubiorev.2022.104970. Epub 2022 Nov 25. PMID: 36436739.
- Santos Palacios S, Pascual-Corrales E, Galofre JC. Management of Subclinical Hyperthyroidism. Int J Endocrinol Metab. 2012;10(2):490-6. DOI: 10.5812/ijem.3447
- Serdenes, R., Lewis, M., & Chandrasekhara, S. (2021). A Clinical Review of the Psychiatric Sequelae of Primary Hyperparathyroidism. *Cureus*, *13*(10), e19078. https://doi.org/10.7759/cureus.19078
- Yu J. Endocrine disorders and the neurologic manifestations. Ann Pediatr Endocrinol Metab. 2014 Dec;19(4):184-90. doi: 10.6065/apem.2014.19.4.184. Epub 2014 Dec 31. PMID: 25654063; PMCID: PMC4316409.

Endocrine and Metabolic Disorders:
A Medical Psychiatry Focus

Medical Psychiatry:
A Comprehensive Update
Sunday, September 21st, 2025

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

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Questions?

cgonzalez7@bwh.harvard.edu