Neuropsychiatry of Endocrine Disorders

CHAPTER 20

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Definition and Aetiology

The bidirectional relationship between endocrine and psychiatric disorders is foundational to the field of psychoneuroendocrinology[1]. These conditions frequently co-occur, complicating diagnosis, treatment, and patient outcomes through a complex brain-immune-endocrine crosstalk that is highly sensitive to psychosocial factors. This chapter reviews the epidemiology, phenomenology, and available pathophysiology of psychiatric syndromes within the most common endocrine disorders: Diabetes mellitus, Thyroid and adrenal disorders, Parathyroid, conditions, and Hyperprolactinemia. By integrating the characteristic physical manifestations of endocrine disorders with their associated psychiatric presentations, this chapter provides clinicians with a practical framework for recognizing, evaluating, and managing these complex clinical conditions.

Major Neuroendocrine Axis

Hypothalamic-Pituitary-Adrenal (HPA) Axis:

The hypothalamic-pituitary-adrenal (HPA) axis is the principal neuroendocrine system regulating the physiologic response to stress. Stress activates the hypothalamus to release corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which stimulate the anterior pituitary to secrete adrenocorticotropic hormone (ACTH). ACTH, in turn, stimulates the adrenal cortex to produce cortisol. Cortisol secretion is regulated by negative feedback at the hypothalamus and pituitary, with additional modulation by glucocorticoid receptors in the hippocampus and medial prefrontal cortex. HPA axis dysregulation has been implicated in several psychiatric disorders. Elevated cortisol is one of the most consistent biological findings in more severe depression with melancholic features, whereas post-traumatic stress disorder (PTSD) is characterized by relatively low peripheral cortisol levels despite elevated central CRH. Similar HPA axis alterations have also been described in other conditions, including hypercortisolemia in anorexia nervosa and blunted HPA axis activity in chronic fatigue syndrome[2].

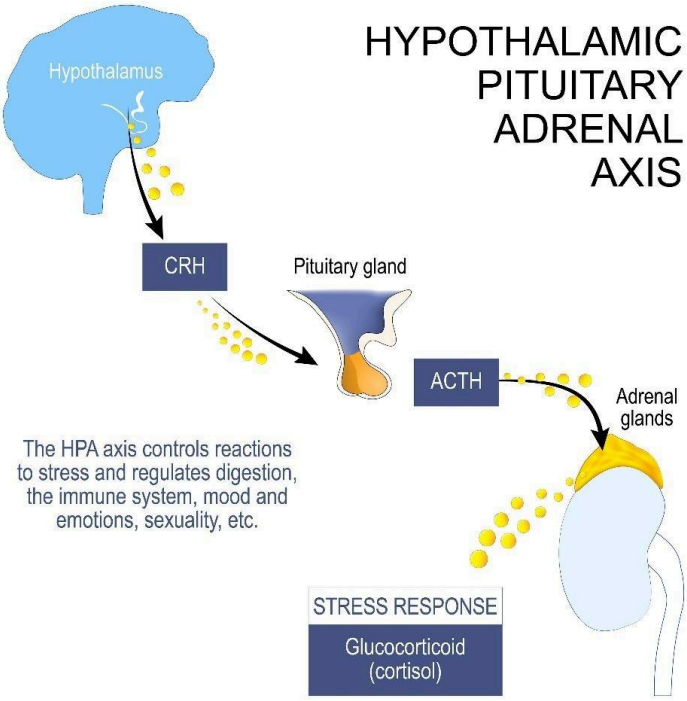


Figure 1. Hypothalamic-Pituitary-Adrenal (HPA) Axis

Hypothalamic-Pituitary-Thyroid (HPT) axis

The Hypothalamic-Pituitary-Thyroid (HPT) axis is the primary neuroendocrine regulator of metabolism, energy homeostasis, thermoregulation, and central nervous system function. It operates through a three-tiered cascade in which hypothalamic thyrotropin-releasing hormone (TRH) stimulates pituitary secretion of thyroid-stimulating hormone (TSH), which in turn promotes thyroid production of thyroxine (T_4) and the biologically active triiodothyronine (T_3). Hormone production is maintained through a sensitive negative feedback loop involving the hypothalamus and pituitary. Within the central nervous system, deiodinase enzymes regulate local thyroid hormone availability by converting T_4 to active T_3 or inactivating thyroid hormones, thereby supporting neurodevelopment, neurotransmission, and synaptic plasticity. Because thyroid hormones influence monoaminergic pathways, neuronal excitability, and adrenergic receptor sensitivity, disturbances of the HPT axis frequently present with psychiatric symptoms. Hypothyroidism, including subclinical disease, commonly manifests with psychomotor slowing, fatigue, anhedonia, impaired concentration, and cognitive dysfunction, whereas hyperthyroidism produces anxiety, irritability, emotional lability, insomnia, and, in severe cases, mania or psychosis[3].

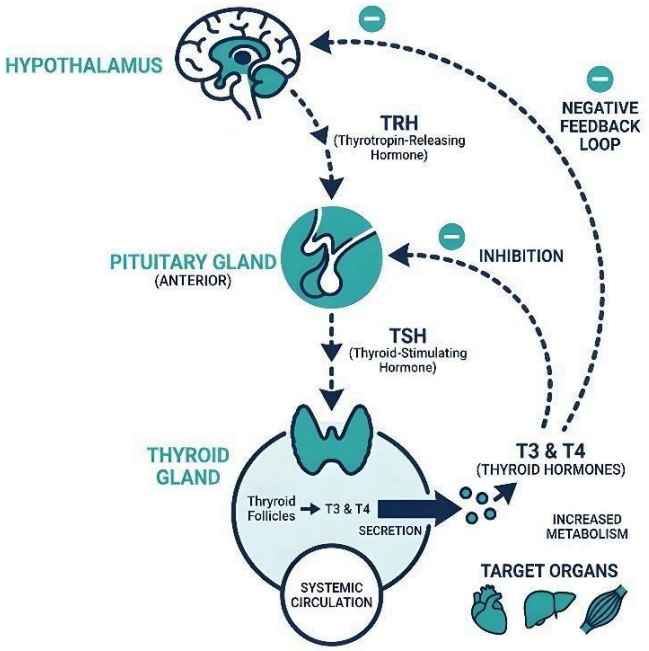


Figure 2. Hypothalamic-Pituitary-Thyroid (HPT) axis

Hypothalamic-Pituitary-Gonadal (HPG) Axis

The Hypothalamic-Pituitary-Gonadal (HPG) axis is the primary neuroendocrine network regulating reproductive function, sexual development, fertility, and sex steroid production. It begins with pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which stimulates the anterior pituitary to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormones act on the ovaries and testes to promote gametogenesis and the production of estrogen, progesterone, and testosterone. Hormone secretion is primarily regulated through negative feedback at the hypothalamic and pituitary levels, although sustained elevations in estradiol produce the positive feedback required for the preovulatory LH surge. Beyond their reproductive functions, gonadal steroids cross the blood-brain barrier and modulate serotonergic, dopaminergic, glutamatergic, and GABAergic neurotransmission, influencing mood, cognition, and stress responsiveness. Consequently, hormonal fluctuations or dysfunction of the HPG axis are associated with distinct neuropsychiatric syndromes. Changes in estrogen and progesterone during the menstrual cycle, pregnancy, the postpartum period, and menopause contribute to mood and anxiety disorders, including Premenstrual dysphoric disorder and postpartum depression, whereas testosterone deficiency in men is associated with depression, fatigue, reduced motivation, and cognitive complaints[4,5].

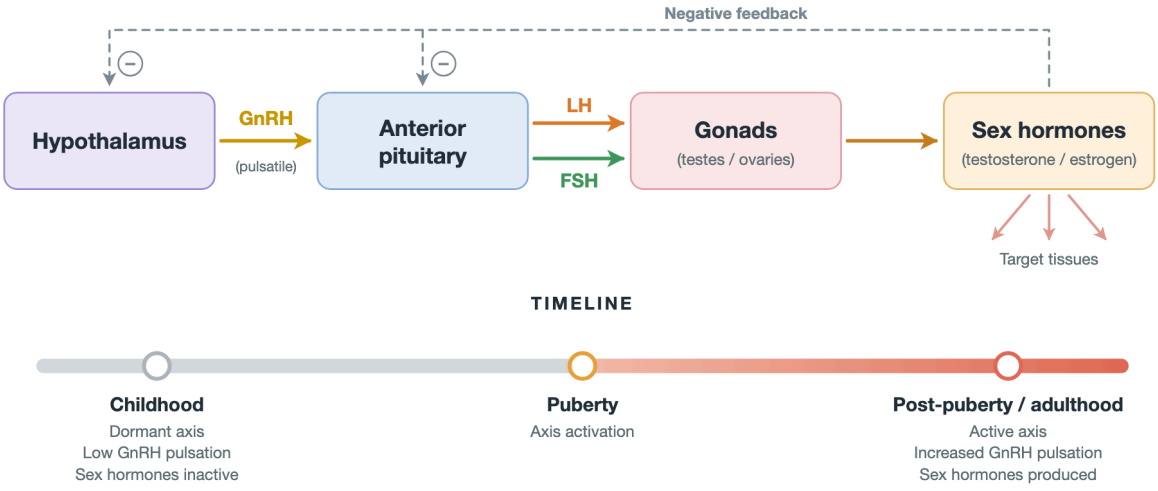


Figure 3. Hypothalamic-Pituitary-Gonadal (HPG) Axis

Diabetes

Diabetes mellitus is characterized by hyperglycemia resulting from deficits in insulin secretion, insulin action, or both. The American Diabetes Association classifies diabetes into four major categories: type 1 diabetes, type 2 diabetes, specific types due to other causes, and gestational diabetes mellitus. Type 2 diabetes accounts for approximately 90–95% of cases[6]. Type 1 diabetes can occur at any age, although it is often diagnosed in childhood, whereas type 2 diabetes is frequently asymptomatic and detected through screening. Classic symptoms include polyuria, polydipsia, weight loss, polyphagia, and blurred vision. Acute complications include diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome, while chronic hyperglycemia increases the risk of retinopathy, nephropathy, peripheral neuropathy, cardiovascular disease, and stroke[7,8].

Diabetes mellitus is strongly associated with a broad spectrum of psychiatric and cognitive disorders through a well-established bidirectional relationship. Individuals with diabetes are at significantly increased risk of developing depression and anxiety, while preexisting psychiatric disorders are themselves associated with an increased risk of incident diabetes[10]. Depression affects approximately one in four individuals with type 1 or type 2 diabetes and occurs nearly twice as often as in the general population. Anxiety disorders are similarly common, with a pooled prevalence of approximately 28% and a 41% greater risk compared with individuals without diabetes[11]. Beyond mood and anxiety disorders, diabetes is now recognized as a major risk factor for cognitive impairment and dementia, including Alzheimer disease, vascular dementia, and the emerging entity of diabetes-related dementia, which appears to have distinct clinical characteristics such as slower progression, long-standing poorly controlled diabetes, and greater frailty[12]. Recognition of these neuropsychiatric complications has led current clinical guidelines to
recommend routine screening for depression, diabetes distress, and anxiety, as well as annual cognitive screening in adults aged 65 years and older with diabetes[13].

Hypothyroidism

Hypothyroidism is characterized by insufficient thyroid hormone production, resulting in generalized slowing of metabolic processes. Primary hypothyroidism accounts for more than 99% of cases and is caused by intrinsic thyroid gland dysfunction. In iodine-sufficient regions, Hashimoto thyroiditis is the leading cause, accounting for up to 85% of cases. Other etiologies include thyroidectomy, radioactive iodine therapy, external-beam radiation, iodine deficiency or excess, and medications such as lithium, amiodarone, immune checkpoint inhibitors, tyrosine kinase inhibitors, and interferon alfa. Transient hypothyroidism may occur following postpartum, subacute, or silent thyroiditis. Central hypothyroidism, resulting from hypothalamic or pituitary disease, accounts for fewer than 1% of cases, while rare peripheral forms include consumptive hypothyroidism and genetic disorders affecting thyroid hormone receptors or transport. Common manifestations include fatigue, weight gain, cognitive impairment, cold intolerance, constipation, dry skin, and hair changes. Although bradycardia, hypothermia, delayed relaxation of deep tendon reflexes, and myxedema are classic findings, symptoms are often nonspecific, and diagnosis is primarily biochemical. Serum thyroid-stimulating hormone (TSH) remains the recommended initial screening test, with high sensitivity and specificity for overt thyroid dysfunction[14,15].

Hypothyroidism is classified as overt or subclinical. In the United States, overt hypothyroidism affects approximately 0.3% of the population, whereas subclinical hypothyroidism affects about 4–5%, with prevalence increasing with age and occurring more commonly in women. Subclinical hypothyroidism is defined by an elevated serum TSH with a normal free thyroxine (fT4) concentration and is further classified as grade 1 (TSH 4.5–9.9 mIU/L), which accounts for approximately 90% of cases, and grade 2 (TSH ≥10 mIU/L). Progression to overt hypothyroidism occurs in approximately 2–6% of patients annually, particularly in those with higher TSH levels or positive thyroid peroxidase antibodies. Because TSH levels rise physiologically with aging, mildly elevated values in older adults may not represent true thyroid disease and may lead to overdiagnosis. Clinically, this distinction is important because adverse cardiovascular outcomes are largely confined to patients with TSH ≥10 mIU/L, whereas grade 1 subclinical hypothyroidism is rarely associated with neuropsychiatric symptoms, and levothyroxine has not been shown to improve depressive symptoms. Similarly, current evidence does not support a consistent association between subclinical hypothyroidism and dementia, cognitive decline, or fracture risk, although subtle working memory deficits have been reported in some patients with grade 2 disease[16].

Hypothyroidism is associated with a broad range of neuropsychiatric manifestations that may involve mood, cognition, anxiety, and, less commonly, psychosis. Patients frequently report fatigue, psychomotor slowing, impaired concentration, memory difficulties, decreased motivation, and depressive symptoms, which may precede recognition of thyroid dysfunction[14]. Depression and anxiety are significantly more common in individuals with overt hypothyroidism and autoimmune thyroid disease[18], whereas the association with subclinical hypothyroidism appears to be weaker and less consistently linked to clinically significant psychiatric symptoms[19,20]. Neuroimaging studies have also demonstrated structural and functional brain changes involving frontal and temporal regions, the hippocampus, and neural connectivity, suggesting that thyroid hormone deficiency may directly affect brain function[21,22].

Most neuropsychiatric symptoms improve with thyroid hormone replacement, although complete resolution is not universal. Approximately 10–15% of patients continue to experience residual fatigue, cognitive complaints, or depressive symptoms despite normalization of thyroid function tests, highlighting the multifactorial nature of persistent symptoms[23]. Rarely, severe untreated hypothyroidism may present with psychosis ("myxedema madness") characterized by persecutory delusions, hallucinations, and cognitive impairment[24,25]. Importantly, psychosis may be the initial presentation of hypothyroidism in patients without a prior thyroid diagnosis and generally responds well to thyroid hormone replacement, often with short-term antipsychotic treatment. These findings underscore the importance of evaluating thyroid function in patients presenting with new-onset depression, cognitive decline, or psychosis.

Hyperthyroidism

Hyperthyroidism is characterized by excessive thyroid hormone production, resulting in a hypermetabolic state affecting multiple organ systems. The most common cause is Graves disease, followed by toxic multinodular goiter and toxic adenoma, although thyrotoxicosis may also result from thyroiditis, exogenous thyroid hormone administration, or immune checkpoint inhibitor therapy. Common manifestations include weight loss despite increased appetite, heat intolerance, palpitations, tremor, diaphoresis, anxiety, insomnia, fatigue, proximal muscle weakness, diarrhea, and menstrual irregularities. Physical examination typically reveals tachycardia, hyperreflexia, warm moist skin, fine tremor, diffuse goiter, and, in Graves disease, ophthalmopathy. Older adults may present with apathetic thyrotoxicosis, characterized by lethargy, depression, and weight loss rather than classic hyperadrenergic symptoms. In severe cases, thyrotoxicosis may progress to thyroid storm, a life-threatening emergency characterized by hyperthermia, tachyarrhythmias, heart failure, delirium, psychosis, coma, and multiorgan dysfunction. [26,27]

Psychiatric manifestations are among the most common neurobehavioral complications of hyperthyroidism and frequently overlap with primary psychiatric disorders. Anxiety, irritability, emotional lability, insomnia, impaired concentration, and depressive symptoms predominate during the acute phase, whereas mania, psychosis, and severe behavioral disturbances are less common. Large population-based studies have consistently demonstrated increased risks of depression, anxiety disorders, bipolar disorder, and sleep disorders in patients with hyperthyroidism, with psychiatric morbidity remaining elevated even after restoration of euthyroidism[20]. Cognitive complaints, including difficulties with attention and memory, are common during active disease, and recent evidence indicates suggests an increased long-term risk of cognitive impairment and dementia[28]. Neuroimaging studies suggest that both thyroid hormone excess and autoimmune mechanisms contribute to structural and functional alterations in brain regions involved in cognition and emotional regulation[29]. Although most psychiatric and cognitive symptoms improve with treatment of the underlying thyroid disorder, some patients continue to experience residual mood or cognitive symptoms, underscoring the need for ongoing psychiatric assessment and management.

Table 1. Neuropsychiatric Manifestations of Thyroid Disease

Condition	Diagnostic Criteria / Labs	Acute/Common Symptoms	Psychiatric Associations	Cognitive/Neuroimaging Findings	Severe/Rare Manifestations
Overt Hypothyroidism	Elevated TSH with low free T4 (fT4)	Fatigue, psychomotor slowing, impaired concentration, memory difficulties, decreased motivation, depressive symptoms	Depression and anxiety significantly more common, especially with autoimmune thyroid disease	Structural/functional changes in frontal and temporal regions, hippocampus, and neural connectivity	"Myxedema madness" — psychosis with persecutory delusions and hallucinations; may be the presenting feature in patients with no prior thyroid diagnosis
Subclinical Hypothyroidism (Grade 1)	TSH 4.5–9.9 mIU/L with normal fT4 (~90% of subclinical cases)	Generally minimal	Not consistently linked to clinically significant psychiatric symptoms; levothyroxine does not improve depressive symptoms	No consistent association with cognitive decline or dementia	None notable
Subclinical Hypothyroidism (Grade 2)	TSH ≥10 mIU/L with normal fT4	Possible subtle deficits	Weaker association than overt disease	Subtle working memory deficits reported in some patients	None notable
Hyperthyroidism (Acute Phase)	Suppressed TSH with elevated thyroid hormones (fT4/T3)	Anxiety, irritability, emotional lability, insomnia, impaired concentration, depressive symptoms	Increased long-term risk of depression, anxiety disorders, bipolar disorder, and sleep disorders — risk persists even after euthyroidism restored	Structural/functional brain alterations in regions involved in cognition and emotional regulation, from both hormone excess and autoimmune mechanisms; increased long-term risk of cognitive impairment and dementia	Mania and psychosis less common but can occur; thyroid storm can cause delirium, psychosis, and coma
Apathetic Thyrotoxicosis (Older Adults)	Same labs as hyperthyroidism (suppressed TSH, elevated fT4/T3), but atypical clinical presentation	Lethargy, depression, weight loss (instead of classic hyperadrenergic picture)	Depression as a presenting feature	Not specified	Not specified

Table 2. Endocrine Disorders with Psychiatric Manifestations

Endocrine Disorder	Underlying Mechanism	Mnemonic	Psychiatric Manifestations
Hyperparathyroidism	Hypercalcemia	"Stones, Bones, Groans, Psychiatric Overtones (and Moans)"	Depression, fatigue, cognitive fog, rarely psychosis

Hypothyroidism	Low T3/T4	"SLUGGISH" — Hypo = HYPOactive brain	Depression, slowed cognition, irritability; severe = "myxedema madness" (psychosis)
Hyperthyroidism	Excess T3/T4	"Racing everything" / Graves' = feeling in GRAVE danger	Anxiety, insomnia, irritability, mimics mania or panic disorder
Cushing's Syndrome	Excess cortisol	"Cushingoid mood swings" — CUSHING (Cortisol, Upset mood, Swings to mania, High anxiety, Insomnia, Neurocognitive slowing, Glucose issues)	Depression (most common), mania (less common), anxiety, insomnia
Addison's Disease	Low cortisol	"Add-ison of apathy" — low everything: low BP, low Na, low mood	Apathy, fatigue, depression, rarely psychosis
Hypoparathyroidism	Hypocalcemia	"CATs go crazy" — Convulsions, Arrhythmias, Tetany + irritability	Anxiety, irritability, seizures; check Chvostek's/Trousseau's signs
Pheochromocytoma	Catecholamine excess	"Pheo = Panic attack mimicker"	Episodic anxiety/panic + headache, palpitations, diaphoresis
Hypoglycemia	Low blood glucose	"Low sugar = Shaky, Sweaty, Scared"	Anxiety, tremor, diaphoresis, irritability — mimics panic attack

Hashimoto's Encephalitis (HE)

Since its original description in 1966, Hashimoto encephalopathy (HE), also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), has remained a controversial diagnosis because its pathophysiology and diagnostic criteria are poorly defined. Diagnosis is further complicated by the high prevalence of thyroid peroxidase (TPO) antibodies in the general population, limiting their specificity. Recent studies show that many patients initially diagnosed with HE are ultimately found to have alternative conditions, including functional neurological disorders, neurodegenerative diseases, or primary psychiatric illnesses. Current evidence supports HE as a rare diagnosis of exclusion requiring encephalopathy, elevated antithyroid antibodies, exclusion of infectious, metabolic, toxic, neoplastic, and other autoimmune causes, and typically a favorable response to corticosteroids. Although anti-NH2-terminal α-enolase (anti-NAE) antibodies may be a more specific biomarker, their use remains largely limited to research settings. Clinicians should therefore interpret positive thyroid antibodies cautiously and avoid attributing neuropsychiatric symptoms to HE without a comprehensive diagnostic evaluation[30, 31, 32].

Cushing's Syndrome

Cushing syndrome results from prolonged exposure to endogenous or exogenous glucocorticoid excess. Endogenous Cushing syndrome is rare, with an incidence of 2–8 cases per million annually, a prevalence of 39–79 per million, and a 3:1 female predominance. The most common manifestations include facial plethora, easy bruising, purple striae, hyperglycemia, hypertension, and centripetal fat redistribution involving the face, dorsocervical region, and visceral organs[33]. Most cases overall are iatrogenic due to glucocorticoid therapy, whereas endogenous disease is classified as ACTH dependent (80–85%) or ACTH independent (15–20%)[34]. Among endogenous causes, Cushing disease caused by a pituitary corticotroph adenoma accounts for 60–70% of cases, followed by adrenal tumors or hyperplasia (20–30%) and ectopic ACTH-secreting tumors (6–10%)[33].

Evaluation begins by excluding exogenous glucocorticoid use. Recommended first-line screening tests include the 24-hour urinary free cortisol, the 1-mg overnight dexamethasone suppression test, and late-night salivary cortisol[35]. Once hypercortisolism is confirmed, plasma ACTH distinguishes ACTH-dependent from ACTH-independent disease. Bilateral inferior petrosal sinus sampling remains the gold standard for differentiating pituitary from ectopic ACTH secretion when pituitary imaging is inconclusive, and advanced imaging modalities may help localize occult lesions[35,36].

Psychiatric manifestations are among the most common features of endogenous Cushing syndrome, with major depression occurring in approximately 50–80% of patients and representing the predominant psychiatric manifestation. Mixed anxiety and depressive symptoms are also common, with anxiety affecting approximately two-thirds of patients. Irritability, emotional lability, and cognitive complaints frequently accompany mood symptoms and often improve following treatment of the underlying endocrine disorder[37]. Although depression and anxiety predominate, mania and psychosis are uncommon but well-recognized complications that typically occur in severe or untreated disease. More recent studies have also reported higher rates of bipolar spectrum disorders than earlier investigations, likely reflecting broader diagnostic criteria encompassing the full bipolar spectrum[38,39].

Cognitive impairment is another hallmark of Cushing syndrome. The Endocrine Society guidelines identify deficits in declarative memory, attention, executive function, working memory, and visuospatial abilities as common manifestations of hypercortisolism, findings supported by recent systematic reviews demonstrating broad neurocognitive impairment across multiple domains[40,41]. Chronic cortisol excess is associated with structural and functional brain abnormalities involving the hippocampus, amygdala, prefrontal cortex, anterior cingulate cortex, and widespread white matter pathways. Although some abnormalities improve after normalization of cortisol levels, recovery is often incomplete, and deficits in memory, executive function, emotional processing, and functional brain connectivity may persist despite biochemical remission[42,43]. Together, these findings indicate that prolonged hypercortisolism produces widespread, only partially reversible alterations in brain structure and function[44].

Glucocorticoid Therapy and Psychiatric Manifestations

Glucocorticoid therapy is associated with a broad spectrum of neuropsychiatric adverse effects. A 2024 systematic review and meta-analysis of 49 studies reported pooled prevalences of depression (22%), mania (11%), anxiety (8%), delirium (16%), and behavioral changes (52%), with depression and mania demonstrating the strongest associations with glucocorticoid exposure[45]. A subsequent 2026 meta-analysis of 73 studies involving more than 3.7 million participants similarly confirmed an increased risk of depressive symptoms, whereas psychotic symptoms occurred in approximately 2.4% of corticosteroid users[46]. Current evidence indicates that depression and mania are the most consistent psychiatric complications of glucocorticoid therapy.

Psychiatric symptoms also demonstrate a characteristic temporal pattern. During the first 8 weeks of treatment, manic and hypomanic symptoms are more common than depression, whereas prolonged corticosteroid therapy is more frequently associated with depressive symptoms[46,47]. A nationwide Swedish cohort study of more than one million individuals similarly found that the risks of anxiety and bipolar disorder were greatest during the first weeks after corticosteroid initiation, highlighting the importance of close psychiatric monitoring early in treatment[48]. The risk of psychiatric adverse effects is dose dependent, increasing substantially at prednisone-equivalent doses above 40 mg/day and peaking at doses greater than 80 mg/day[49] More recent studies confirm that higher daily glucocorticoid doses are associated with more severe depressive symptoms, although cumulative dose and treatment duration appear to have less influence[49]. More recent studies confirm that higher daily glucocorticoid doses are associated with more severe depressive symptoms, although cumulative dose and treatment duration appear to have less influence[46]. Clinically significant psychiatric symptoms may also occur with moderate doses, particularly in medically complex populations such as patients with cancer, suggesting that individual susceptibility and comorbid conditions contribute substantially to risk[50].

Adrenal Insufficiency

The clinical manifestations of adrenal insufficiency may be chronic or acute. Chronic adrenal insufficiency develops insidiously and commonly presents with fatigue, weakness, anorexia, weight loss, nausea, abdominal discomfort, orthostatic hypotension, and hyperpigmentation in primary adrenal insufficiency. Salt craving is a distinguishing feature of primary adrenal insufficiency because of mineralocorticoid deficiency, and women may experience loss of axillary and pubic hair due to adrenal androgen deficiency[51]. Depression, anxiety, irritability, and cognitive impairment are increasingly recognized manifestations. Patients with Addison disease have a 2.68-fold increased risk of affective disorders and a 2.12-fold increased risk of depression compared with the general population[52]. Cognitive deficits, particularly involving memory and executive function, are thought to result from impaired glucocorticoid and mineralocorticoid signaling within the hippocampus and prefrontal cortex, as well as the inability of current replacement regimens to reproduce physiologic cortisol secretion[53,54]. Despite adequate hormone replacement, many patients continue to report fatigue, depression, anxiety, impaired quality of life, and reduced functional capacity, with approximately half considering themselves unfit to work.

Common laboratory abnormalities include hyponatremia, hyperkalemia, anemia, eosinophilia, lymphocytosis, and, less commonly, hypoglycemia[55]. Because symptoms are often nonspecific and develop gradually, diagnosis is frequently delayed[56].

Acute adrenal insufficiency (adrenal crisis) is a life-threatening endocrine emergency characterized by severe weakness, abdominal pain, nausea, vomiting, fever, hypotension, altered mental status, delirium, and hypovolemic or distributive shock. Severe hyponatremia may contribute to confusion, seizures, and coma. Up to 50% of patients with primary adrenal insufficiency present initially with adrenal crisis, and 6–8% experience recurrent crises annually despite treatment[55].

Primary adrenal insufficiency is most commonly caused by autoimmune adrenalitis, accounting for approximately 90% of cases in Western countries, with clinical disease developing only after destruction of nearly 90% of the adrenal cortex. Immune checkpoint inhibitors have emerged as an important cause of both primary and secondary adrenal insufficiency in oncology patients, while chronic opioid therapy is now recognized as a cause of secondary adrenal insufficiency through suppression of corticotropin secretion[51].

Pheochromocytomas

Pheochromocytomas are rare catecholamine-secreting neuroendocrine tumors arising from chromaffin cells of the adrenal medulla, whereas extra-adrenal tumors are classified as paragangliomas. Their annual incidence is 2–8 cases per million, and they account for fewer than 0.1% of cases of hypertension[57]. Approximately 80–85% are adrenal pheochromocytomas and 15–20% are extra-adrenal paragangliomas[58,59]. Clinical manifestations result from catecholamine excess and include episodic hypertension, headache, palpitations, diaphoresis, tremor, tachycardia, pallor, and anxiety. Although the classic triad of headache, palpitations, and diaphoresis is traditionally associated with pheochromocytoma, it is present in only 12–24% of patients, as many tumors are now detected incidentally during imaging performed for unrelated indications[60]. Clinicians should therefore maintain a high index of suspicion in patients with unexplained paroxysmal hypertension, autonomic symptoms, or recurrent panic-like episodes.

Diagnosis is based on biochemical evidence of catecholamine excess, with plasma free or 24-hour urinary fractionated metanephrines serving as the preferred screening tests[61]. Several medications, including tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, antipsychotics, and levodopa, may cause false-positive results. Approximately 30–40% of patients harbor a germline pathogenic variant, and current guidelines recommend genetic counseling and multigene panel testing for all patients because of implications for surveillance and family screening[62].

All pheochromocytomas and paragangliomas have metastatic potential, with approximately 25% of patients ultimately developing metastatic disease. Germline SDHB pathogenic variants are associated with the highest metastatic risk and warrant closer long-term surveillance[63].

Psychiatric manifestations are common, with anxiety affecting approximately 20–40% of patients and representing the predominant psychiatric symptom[64,65]. Depression is also increasingly recognized, whereas psychosis is rare and usually resolves following tumor resection. Catecholamine surges often produce panic-like episodes characterized by palpitations, diaphoresis, tremor, and intense anxiety; when directly attributable to catecholamine excess, these episodes are more

appropriately classified as anxiety disorder due to another medical condition rather than primary panic disorder[66]. Acute pheochromocytoma crisis may present with delirium, seizures, stroke, or reversible cerebral vasoconstriction syndrome[67]. Pheochromocytoma should therefore be considered in patients with recurrent panic-like episodes accompanied by autonomic instability or paroxysmal hypertension.

Hyperprolactinemia

Prolactin is secreted by lactotroph cells of the anterior pituitary and is primarily regulated by hypothalamic dopamine. Hyperprolactinemia most commonly results from prolactin-secreting pituitary adenomas, dopamine-blocking medications (particularly antipsychotics), antidepressants, opioids, metoclopramide, primary hypothyroidism, chronic kidney disease, cirrhosis, and polycystic ovary syndrome. Compression of the pituitary stalk ("stalk effect") and macroprolactinemia should also be considered in the differential diagnosis. Clinically, hyperprolactinemia commonly presents with menstrual irregularities, infertility, decreased libido, erectile dysfunction, and galactorrhea, and long-standing disease may lead to osteoporosis and cognitive dysfunction involving memory, attention, and executive function[68]. Psychiatric symptoms are common, with anxiety affecting approximately 54% of women and depression reported in both sexes; symptoms often improve following treatment with dopamine agonists.

The diagnosis is established by demonstrating an elevated serum prolactin concentration after excluding physiologic and secondary causes. Mild elevations should be confirmed with repeat testing. Serum prolactin levels also provide diagnostic clues, with concentrations >250 ng/mL strongly suggesting a prolactinoma, whereas lower levels more commonly reflect medication effects, systemic illness, or stalk compression. Drug-induced hyperprolactinemia is now the leading cause, accounting for approximately 46% of cases[69,70].

Antipsychotic medications are among the most common causes of hyperprolactinemia because of dopamine D_2 receptor blockade in the tuberoinfundibular pathway. The risk varies substantially by agent, with risperidone and amisulpride carrying the highest risk, followed by paliperidone, ziprasidone, and haloperidol, whereas quetiapine, clozapine, brexpiprazole, cariprazine, lumateperone, and particularly aripiprazole have minimal effects on prolactin[71,72].

For prolactinomas, cabergoline is the preferred first-line treatment because of its superior efficacy and tolerability compared with bromocriptine. It normalizes prolactin levels in most patients, induces tumor shrinkage in approximately 70%, and remains effective in the majority of cases, although dopamine agonist resistance occurs in up to 15% of patients[73,74]. Clinicians should monitor for rare psychiatric adverse effects of dopamine agonists, including impulse control disorders, mania, depression, and psychosis, which are typically reversible after dose reduction or discontinuation. Cabergoline withdrawal may be considered after prolonged biochemical remission, although long-term remission is achieved in only a minority of patients[75].

Hyperparathyroidism

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder after diabetes mellitus and hypothyroidism, affecting approximately 1% of adults and up to 2–3.4% of postmenopausal women[76]. In developed countries, most patients are asymptomatic or present with nonspecific symptoms rather than the classic "stones, bones, groans, and psychiatric overtones." Common manifestations include fatigue, weakness, impaired concentration, memory complaints, sleep disturbance, depression, anxiety, musculoskeletal pain, and gastrointestinal symptoms, many of which improve after parathyroidectomy[77]. PHPT is more common in women and is caused by a solitary parathyroid adenoma in approximately 80% of cases, multigland disease in 10–20%, multiple adenomas in 10–11%, and parathyroid carcinoma in fewer than 1%; hereditary syndromes account for 5–10% of cases[78].

A recognized variant, normocalcemic primary hyperparathyroidism (NPHPT), is characterized by persistently elevated parathyroid hormone (PTH) levels despite normal serum calcium after secondary causes have been excluded[79]. The diagnosis of PHPT is biochemical, requiring hypercalcemia (or normocalcemia in NPHPT) with an elevated or inappropriately normal PTH concentration. Evaluation should include serum creatinine, 25-hydroxyvitamin D, and 24-hour urinary calcium to exclude familial hypocalciuric hypercalcemia. Although osteitis fibrosa cystica is now uncommon, osteoporosis, fragility fractures, and nephrolithiasis remain major complications[80].

Neuropsychiatric symptoms are increasingly recognized as important manifestations of PHPT and include depression, anxiety, fatigue, sleep disturbance, impaired concentration, memory complaints, and reduced quality of life. Approximately 28% of patients report moderate-to-severe depressive symptoms and 18% report moderate-to-severe anxiety before surgery[81]. Parathyroidectomy is associated with significant improvements in depression, anxiety, cognition, and quality of life, findings confirmed by multiple prospective studies and meta-analyses[82,83]. More recent population-based studies suggest that surgery reduces the risk of new-onset cognitive impairment and somnolence, although its long-term effects on anxiety and depression are less consistent[84].

Parathyroidectomy is the definitive treatment for PHPT and is recommended for symptomatic patients and selected asymptomatic individuals meeting guideline criteria[79]. Although neuropsychiatric symptoms are increasingly recognized as manifestations of PHPT, their role as independent indications for surgery remains controversial. Current guidelines acknowledge that these symptoms may support surgical intervention in appropriately selected patients but continue to prioritize biochemical, skeletal, and renal indications[85,86].

Hypoparathyroidism

Hypoparathyroidism is characterized by deficient parathyroid hormone (PTH) secretion, resulting in hypocalcemia, hyperphosphatemia, and hypercalciuria. Postsurgical injury is the most common cause, accounting for approximately 78% of cases, with autoimmune, genetic, infiltrative, and idiopathic etiologies comprising the remainder[87,88]. The estimated prevalence is 23–37 per 100,000[89]. Clinical manifestations primarily reflect hypocalcemia and include paresthesia, muscle cramps,

carpopedal spasm, laryngospasm, seizures, QT prolongation, and, in severe cases, torsade's de pointes. Long-term complications include nephrocalcinosis, nephrolithiasis, renal insufficiency, cataracts, and basal ganglia calcification[88–91].

Psychiatric and cognitive manifestations are now recognized as major contributors to disease burden. A large multicenter study found significantly higher rates of depression and anxiety in patients with hypoparathyroidism than in healthy controls, with most patients reporting persistent symptoms despite established treatment[92]. Population-based studies have similarly demonstrated worse cognitive and emotional functioning, particularly fatigue, impaired concentration, pain, and paresthesias, with women reporting the greatest symptom burden[93]. Objective neuropsychological testing has identified deficits in processing speed, executive function, visual and auditory memory, while neuroimaging studies have demonstrated reduced hippocampal volume associated with cognitive impairment and "brain fog."[87,94] Longitudinal data further suggest progressive decline in cognitive performance over time, although intracranial calcification does not appear to predict neuropsychiatric outcomes[95].

Conventional therapy with oral calcium and active vitamin D effectively corrects hypocalcemia but often fails to fully restore quality of life or cognitive function[87,88]. The treatment landscape has changed with the introduction of PTH replacement therapy. Palopegteriparatide (TransCon PTH) and recombinant human PTH have demonstrated significant improvements in biochemical control, symptom burden, physical functioning, and health-related quality of life while reducing dependence on conventional calcium and vitamin D therapy[87,96–100]. Although evidence for improvements in cognition remains limited, PTH replacement represents an important advance in the long-term management of chronic hypoparathyroidism.

Table 3. Screening Mnemonic (PACT) — Organic Causes to Rule Out Before a Psychiatric Diagnosis

Letter	System to Check
P	Parathyroid/calcium (both directions)
A	Adrenal medulla (pheo) and blood glucose (hypoglycemia)
C	Cortisol (Cushing's and Addison's)
T	Thyroid (hypo- and hyper-)

Conclusion

Over the past decade, substantial advances have transformed our understanding of the relationship between endocrine disorders and psychiatric illness. Current evidence demonstrates that psychiatric manifestations are not simply secondary reactions to chronic medical disease but reflect complex interactions among hormonal dysregulation, immune activation, genetic susceptibility, and alterations in brain structure and function. Large epidemiologic, genetic, and neuroimaging studies have shown that depression, anxiety, and cognitive impairment are common across many endocrine disorders and often represent core features of the underlying disease.

An important clinical observation is that psychiatric symptoms do not always resolve after normalization of endocrine function. Patients with disorders such as Cushing syndrome, thyroid disease, diabetes mellitus, and primary hyperparathyroidism may continue to experience depression, anxiety, fatigue, cognitive impairment, and reduced quality of life despite successful endocrine treatment. These findings underscore the need for routine psychiatric screening, evidence-based treatment, and close collaboration among endocrinologists, psychiatrists, psychologists, and primary care clinicians.

Although major progress has been made in defining the biological mechanisms linking endocrine and psychiatric disorders, important questions remain regarding individual vulnerability, the persistence of psychiatric symptoms after endocrine remission, and the development of personalized therapies. Future research integrating genetic, immunologic, neuroimaging, and biomarker data will further advance precision medicine and improve outcomes for patients with these interconnected disorders.

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