Biology of Psychiatric Disorders

Chapter 462 | Harrison's 22e

KEY CLINICAL POINTS

1. Psychiatric disorders are heterogeneous syndromes currently lacking well-defined neuropathology and specific biological markers; diagnosis relies on clinical observation via DSM-5 criteria.
2. The Research Domain Criteria (RDoC) framework addresses the limitations of categorical nosology by focusing on core behavioral abnormalities (e.g., psychosis, anhedonia) and underlying brain circuitry.
3. Neurogenetics provides critical insights into pathogenesis; germline risk alleles are key for distinguishing etiological factors from compensatory responses.
4. Autism Spectrum Disorders (ASD) are highly heritable (60–90% monozygotic twin concordance) and characterized by polygenic inheritance ('conspiracy of alleles').
5. Opioid action in the locus coeruleus (LC) involves μ-opioid receptors, G_i/G_o proteins, and the cAMP-PKA-CREB pathway; chronic use leads to homeostatic upregulation of AC isoforms, PKA subunits, and tyrosine hydroxylase.
6. Advanced tools like GWAS, high-throughput sequencing, and patient-derived iPSC-derived brain organoids are accelerating the study of psychiatric pathophysiology.

DEFINITION & CLASSIFICATION

- **Current Clinical Status:** Psychiatric disorders are broad, heterogeneous syndromes.
  - **Pathology:** Currently lack well-defined neuropathology and bona fide biological markers.
  - **Diagnosis:** Based solely on clinical observations using criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).
- **Alternative Framework:** Research Domain Criteria (RDoC).
  - **Purpose:** Addresses limitations of categorical nosology by focusing on core behavioral abnormalities shared across several syndromes.
  - **Key Domains:** Includes psychosis (loss of reality) and anhedonia (decreased ability to experience pleasure) and the associated brain circuitry controlling these behaviors.

ETIOLOGY & PATHOPHYSIOLOGY

- **Neurogenetics:** Essential for identifying molecular clues since the human brain can only be examined indirectly during life.
  - **Germline Risk:** Identification of germline risk alleles/mutations allows distinction between etiological factors and compensatory responses (germline risk is present before the brain develops).
  - **Methodologies:** Progress driven by genome-wide association studies (GWAS), high-throughput sequencing, and patient-derived pluripotent stem cells (iPSCs) to create brain organoids.
- **Genetics of Autism Spectrum Disorders (ASD):**
  - **Heritability:** Highly heritable; monozygotic twin concordance is 60–90% (a 4- to 6-fold increase compared to dizygotic twins).

– **Inheritance Pattern:** Polygenic; characterized by a "conspiracy of alleles" that are common in the population but carry small individual effects.

– **Molecular Findings:** Enrichment of pre- and postsynaptic molecules and chromatin modifiers.

– **Developmental Convergence:** Identified in deep layer (V and VI) excitatory neurons in mid-fetal human cortex; also noted in glutamatergic neurons in mid-fetal prefrontal cortex.

CLINICAL FEATURES

- **Course and Prognosis:**
  – **Severity:** Ranges from mild/moderate (varying degrees of pre-illness function) to severe (patients essentially homebound).
  – **Progression:** Most patients experience some improvement; however, return to prior level of function is unusual.
  – **Warning Signs:** A continued decline in function should prompt evaluation for other illnesses.
- **Specific Risks (e.g., ME/CFS):**
  – **Symptoms:** Social isolation, loss of hope, serious depression, and increased risk of suicide.

DIAGNOSTIC APPROACH

- **Clinical Observation:** Diagnosis is made based on DSM-5 criteria.
  – **Symptom Monitoring:** New or changing symptoms → work up to identify any new illnesses.
  – **Scheduled Intervals:** Used to adjust treatments and detect intercurrent disease.

MANAGEMENT & TREATMENT

- **Supportive Care:** Counseling may help patients and their families cope with the long-term consequences of chronic illness.
  – **Rehabilitation:** Consultation with physical or occupational therapists to identify energy-saving strategies and necessary accommodations (e.g., wheelchairs for limited mobility).

BIOLOGICAL MECHANISMS

- **Opioid Action in the Locus Coeruleus (LC):**
  – **Acute Mechanism:** μ-opioid receptor → G_i/G_o proteins → inhibition of adenylyl cyclase (AC) → reduced cAMP → reduced PKA activity → reduced phosphorylation of CREB.
  – **Chronic Adaptation:** Chronic administration leads to homeostatic upregulation of:

1. AC isoforms.
2. PKA catalytic (C) and regulatory (R) subunits.
3. Tyrosine hydroxylase (the rate-limiting enzyme in catecholamine biosynthesis).
   – **Result:** Increased excitability of LC neurons due to enhanced cAMP signaling.

REFERENCE TABLES

TABLE 462-1

Initial Actions of Drugs of Abuse DRUG Opioids Psychostimulants (cocaine, amphetamine, methamphetamine) Nicotine Ethanol

DRUG	NEUROTRANSMITTER AFFECTED	DRUG TARGET (ACTION)
Opioids	Endorphins, enkephalins	μ- and δ-opioid receptors (agonist)
	Dopamine	
Nicotine	Acetylcholine	Nicotinic cholinergic receptors (agonist)
	GABA	
	Glutamate	
	Acetylcholine	
	Serotonin	
	Others	
Marijuana	Endocannabinoids (anandamide, 2-arachidonoylglycerol)	CB receptor (agonist) 1
	Glutamate	