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Counseling may help patients and their families cope with the long-term consequences of living with a chronic illness. Consulta tion with a physical or occupational therapist may identify energysaving strategies for activities of daily living as well as needed accommodations, such as a wheelchair for activities that require walking longer distances or prolonged standing. COURSE AND PROGNOSIS The illness severity varies from mild or moderate, with patients retaining varying degrees of pre-illness function, to severe, with patients essentially homebound. Most patients experience some improvement and stabilize, although return to their prior level of function is unusual. A continued decline in function should prompt evaluation for other illnesses. Patients should be re-evaluated at scheduled intervals to adjust treatments and detect any intercur rent disease. New or changing symptoms should be worked up to identify any new illnesses. Given the social isolation and loss of hope associated with a debilitating chronic illness, serious depres sion and an increased risk of suicide are reported for patients with ME/CFS. Clinicians should be prepared to screen for this and refer patients as needed. ■ ■FURTHER READING Centers for Disease Control and Prevention: Myalgic enceph alomyelitis/chronic fatigue syndrome (ME/CFS). Available from https://www.cdc.gov/me-cfs/about/index.html. Accessed June 4, 2024. Choutka J et al: Unexplained post-acute infection syndromes. Nat Med 28:911, 2022. Grach SL et al: Diagnosis and management of myalgic encephalomy elitis/chronic fatigue syndrome. Mayo Clin Proc 98:1544, 2023. Institute of Medicine: Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington, DC: The National Academies Press, 2015. Komaroff AL et al: ME/CFS and Long COVID share similar symp toms and biological abnormalities: Road map to the literature. Front Med (Lausanne) 10:1187163, 2023. Lapp CW: Initiating care of a patient with myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS). Front Pediatr 6:415, 2019. Rowe PC et al: Myalgic encephalomyelitis/chronic fatigue syndrome diagnosis and management in young people: A primer. Front Pediatr 5:121, 2017. Vahratian A et al: Myalgic encephalomyelitis/chronic fatigue syndrome in adults: United States, 2021-2022. NCHS Data Brief 488:1, 2023. Walitt B et al: Deep phenotyping of post-infectious myalgic encepha lomyelitis/chronic fatigue syndrome. Nat Commun 15:907, 2024. Section 5 Psychiatric and Addiction Disorders Robert O. Messing, Eric J. Nestler,

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Biology of Psychiatric

Disorders Psychiatric disorders are central nervous system diseases characterized by disturbances in emotion, cognition, motivation, and socialization. They are highly heritable, with genetic risk comprising 20–90% of disease vulnerability depending on the syndrome. As a result of their

prevalence, early onset, and persistence, they contribute substantially to the burden of illness worldwide. All psychiatric disorders are broad heterogeneous syndromes that currently lack well-defined neuropa thology and bona fide biologic markers. Therefore, diagnoses continue to be made solely from clinical observations using criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), of the American Psychiatric Association (see Chap. 463).

There is increasing agreement that the classification of psychiatric illnesses in the DSM does not accurately reflect their underlying biol ogy. Uncertainties in diagnosis complicate efforts to study the genetic basis and attendant neurobiological mechanisms underlying mental illness, though recent technologic advances along with the consoli dation of very large patient cohorts have, for multiple disorders, led to significant progress in these realms. In addition, there have been efforts to address the limitations of a categorical nosology directly through the development of an alternative diagnostic scheme, termed Research Domain Criteria (RDoC). This system classifies mental ill ness on the basis of core behavioral abnormalities shared across several syndromes—such as psychosis (loss of reality) or anhedonia (decreased ability to experience pleasure)—and the associated brain circuitry that controls these behavioral domains. Such classifications may assist in defining the biologic basis of key symptoms. Other factors that have impeded progress in understanding mental illness include the lack of access to pathologic brain tissue except upon death and inherent limitations of animal models for disorders defined largely by behavioral abnormalities (e.g., hallucinations, delusions, guilt, suicidality) that are inaccessible in animals. CHAPTER 462 Biology of Psychiatric Disorders Despite these limitations, the past decade has been marked by real progress. Neuroimaging methods are beginning to provide evidence of brain pathology; genome-wide association studies and high-throughput sequencing are reliably identifying genes and genomic loci that confer risk for severe forms of mental illness; and investigations of bettervalidated animal models, leveraging a host of new methods to study molecular, cellular, and circuit-level processes, are offering new insight into disease pathogenesis. There is also excitement in the utility of neurons, glia, and brain organoids induced in vitro from patientderived pluripotent stem cells, providing novel ways to study disease pathophysiology and screen for new treatments. There is consequently justified optimism that the field of psychiatry will better integrate behaviorally defined syndromes with an understanding of biological substrates in a way that will drive the development of improved treat ments and eventually cures and preventive measures. This chapter describes several examples of recent discoveries in basic neuroscience and genetics that have informed our current understanding of disease mechanisms in psychiatry. ■ ■NEUROGENETICS Because the human brain can only be examined indirectly during life, genome analyses have been extremely important for obtaining molecu lar clues about the pathogenesis of psychiatric disorders. Moreover, the identification of germline risk alleles and mutations provides potential traction on the question of cause versus effect. In other types of crosssectional studies, it may be impossible to determine whether a phe notype or biomarker observed in affected humans or model systems reflects an etiologic factor or a compensatory response. In contrast, germline

genetic risk is present before the brain develops—at least theoretically allowing for experiments to address temporal sequencing. A wealth of new information has been made possible by two decades of advances subsequent to the sequencing of the human genome. These have enabled affordable, very large-scale genome-wide association and high-throughput sequencing studies. A striking example of the impact of these developments has been progress in the genetics of autism spectrum disorders (ASDs), a phenotypically heterogeneous neurodevelopmental syndrome characterized by impaired social com munication and restricted, repetitive patterns of behavior. ASDs are highly heritable. Concordance rates in monozygotic twins range from 60–90%, a four- to sixfold increase compared to dizygotic twins and siblings. ASDs are also highly genetically heterogeneous and, like many psychiatric conditions, are mainly inherited in a polygenic fashion,

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