Borderline personality disorder (BPD) is a severe psychiatric illness affecting 2 to 3 percent of the population. It is marked by pervasive instability in interpersonal relationships, moods, behavior, and self-image, and although it commonly co-occurs with major depressive disorder, it is often more subjectively severe, with distinct symptoms and treatment responses.

Dialectical-behavioral therapy, developed in the late 1980s as a therapy for patients who are chronically suicidal, is the most widely practiced of the empirically validated treatments for BPD, and in multiple controlled trials, it proved superior to treatment as usual for BPD across most domains. But a pivotal study, published in *The American Journal of Psychiatry* in 2009, found that general psychiatric management—a combination of psychodynamically informed therapy and symptom-targeted medication management—was as effective at reducing suicidal and self-injurious episodes and other BPD symptoms as dialectical-behavioral therapy was.

Brian A. Palmer, M.D., M.P.H., a psychiatrist specializing in borderline personality disorder and psychiatric education at Mayo Clinic’s campus in Rochester, Minnesota, says general psychiatric management, when delivered by psychiatrists experienced in BPD using specific techniques and approaches, can provide care on a par with more-expensive and intensive dialectical-behavioral therapy. “The reality is that good treatment can and usually does result in significant improvement in patients with this misunderstood disorder, whereas poor treatment is unhelpful and can make patients worse,” he explains.

Dr. Palmer, who trains psychiatrists in the general psychiatric management of BPD based on the pioneering work of John G. Gunderson, M.D., describes three common mistakes clinicians make: treatment of mood symptoms only, lack of treatment goals, and failure to anticipate and understand BPD challenges.

**Treatment of mood symptoms only**

“At its core, BPD is an interpersonal disorder,” he says. “A common mistake is focusing on the mood symptoms without appreciating the interpersonal context in which they occur. Depression is unlikely to improve until BPD improves, and BPD is the single largest cause of persistent depression.” Dr. Palmer and co-author Kei Yoshimatsu described the unique features and clinical trajectory of BPD depression in an article published in *Harvard Review of Psychiatry* in 2014.

**Lack of treatment goals**

Good psychiatric management teaches that continued therapy is contingent on progress during treatment. But Dr. Palmer says the dictate is often ignored because clinicians fear it will trigger the fear of abandonment common in patients with BPD. “Anchoring the treatment in goals outside the therapeutic relationship helps guard against complicity with the patient’s avoidance of work or school and helps ensure that treatment is accountable for progress,” he explains.

Another obstacle is the common misconception that patients with BPD rarely get better—even driven by a sampling error in
The heritability of bipolar disorder — a severe mood disorder characterized by recurrent episodes of mania or hypomania and depression — has been estimated at around 85 percent. In the last decade, replicated genome-wide association studies have identified several risk loci, most notably ANK3, NCAN, CACNA1C and ODZ4. Genes associated with circadian rhythm patterns, including circadian locomotor output cycles kaput (CLOCK) genes, have also been linked to bipolar disorder.

Although these studies have provided valuable information about the molecular mechanisms of bipolar disorder, they don’t fully explain its heritability, which is likely the result of a large number of risk genes, each conferring a small degree of disease susceptibility. Thus, more research is needed, ideally using large patient populations with precisely defined phenotypes.

To further this aim, Mayo Clinic in Rochester, Minnesota, established a bipolar biobank in collaboration with the Lindner Center of HOPE and the University of Minnesota in 2009. The goal was to create a resource for clinical and biomarker studies of disease risk and treatment response.

To date, nearly 2,000 patients have contributed medical information and blood samples to the biobank. Most participants are white and...
female, with diagnosed bipolar I disorder. Clinical phenotypes include a history of psychosis, attempted suicide, nicotine or alcohol addiction, and antidepressant-induced mania. Nearly 43 percent of biobank patients met the criteria for obesity (body mass index of 30 or higher).

Genetic variation regulated by BMI
The obesity phenotype has proved a fruitful area of research, according to biobank co-principal investigator and lead statistical geneticist, Joanna M. Biernacka, Ph.D., who directs the Psychiatric Genomics and Pharmacogenomics Program at Mayo Clinic’s campus in Minnesota.

“The way in which some genetic variations associated with bipolar disorder impact disease presentation appears to be regulated by factors related to BMI,” she explains. “Our research group found that rs12772424 — a variant of the gene-encoding TCFL2 — may help mediate the onset of bipolar disorder. The effect of the gene increases with body mass index (BMI), which may reflect the role of psychiatric comorbidities such as binge-eating disorder.”

The group’s initial finding was published in Molecular Psychiatry in 2014; the replication was published in Bipolar Disorders in 2016. A related 2016 study published in the Journal of Affective Disorders found an increased prevalence of obesity and binge-eating disorder in patients with bipolar disorder.

Still, the precise relationship between obesity and bipolar disorder remains unclear, says Mark A. Frye, M.D., the biobank’s other principal investigator and a psychiatrist specializing in bipolar disorder at Mayo Clinic’s campus in Minnesota. “Was there an elevated BMI from the beginning? Did the BMI increase over time? We want to better understand the genetic risk and interaction with obesity, yet it’s very challenging due to the complexity of this disease,” he says.

Nevertheless, Dr. Frye says the detailed phenotype obtained for biobank participants is an important research tool. He points out that composite measures of mood instability, comorbid anxiety and multiple drug addiction, beyond the confirmed bipolar disorder subtype, are novel quantifications that may provide more-detailed clinical disease characteristics that can be used in future biomarker genomic studies.

“For future studies that focus not on a DSM-5 bipolar disorder diagnosis but on a more-detailed phenotype such as bipolar disorder with obesity may uncover risk genes not previously identified,” he explains.

For more information


Epigenetic Gene Regulation May Play Role in Psychiatric Disorders

Schizophrenia, bipolar disorder and other psychiatric disorders are complex illnesses in which neural circuit structure and function are altered. Although inheritance plays an important role in the etiology of these conditions, the 50 to 70 percent concordance rates among identical twins indicate that environmental factors are also involved. Evidence increasingly suggests that these changes are maintained by epigenetic modifications, especially DNA methylation, according to Marin Veldic, M.D., a psychiatrist and epigenetics researcher at Mayo Clinic’s campus in Rochester, Minnesota.

DNA methylation — the addition of a methyl group on the cytosine of CpG dinucleotides — may alter gene expression by restricting access of transcription factors to promoter regions or changing mRNA processing. Although these alterations don’t change the genetic code, they are long lasting and may be heritable.

Methylation studies
Most of what is known about the role of DNA methylation in schizophrenia and other psychiatric disorders is based on studies of postmortem brain tissue, peripheral blood or both. Dr. Veldic co-authored a study published in Schizophrenia Research in 2009 that found overexpression of both DNA-methyltransferase-1 (DNMT-1) and DNMT3a mRNA — but not DNMT3b — in cortical GABAergic neurons in patients with schizophrenia, leading to promoter hypermeth-
ylation. A twofold increase of DNMT-1 and DNMT3a mRNA was also observed in peripheral blood lymphocytes. Conversely, a 2013 study published in *Alcoholism: Clinical and Experimental Research* found that the increase in DNMT-1 was reversed in patients with schizophrenia or bipolar disorder who had a history of excessive alcohol use. Dr. Veldic suggests that alcohol addiction may represent a form of acquired comorbidity for some patients. More recently, large methylome- and epigenome-wide association studies have used next-generation sequencing to identify schizophrenia methylation biomarkers in blood. A study published in *JAMA Psychiatry* in 2014 reported alterations in methylation of genes related to hypoxia and infection, two risk factors in early life associated with later schizophrenia. And a 2016 epigenome-wide association study, also in *JAMA Psychiatry*, identified 172 replicated sites of altered methylation in patients with schizophrenia.

Dr. Veldic says the growing number of high-quality methylation studies can advance mental health research in several important ways. For example, it may be possible to identify disease subtypes using easily obtained blood biomarkers that would allow for earlier or more precise diagnosis. Methylation studies can also generate hypotheses about disease mechanisms. And methylation sites in the brain that are reflected in peripheral blood may help confirm that environmental factors can affect methylation in many areas, not just brain tissue.

“The whole field is growing enormously,” Dr. Veldic says. “When I was starting out more than 15 years ago, there were just a few papers — now there are hundreds, and this research will have a significant clinical and translational impact.”

**For more information**


