The State of Our Understanding of the Pathophysiology and Optimal Treatment of Depression: Glass Half Full or Half Empty?

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Major depressive disorder is a remarkably common and often severe psychiatric disorder associated with high levels of morbidity and mortality. Patients with major depression are prone to several comorbid psychiatric conditions, including posttraumatic stress disorder, anxiety disorders, obsessive-compulsive disorder, and substance use disorders, and medical conditions, including cardiovascular disease, diabetes, stroke, cancer, which, coupled with the risk of suicide, result in a shortened life expectancy. The goal of this review is to provide an overview of our current understanding of major depression, from pathophysiology to treatment. In spite of decades of research, relatively little is known about its pathogenesis, other than that risk is largely defined by a combination of ill-defined genetic and environmental factors. Although we know that female sex, a history of childhood maltreatment, and family history as well as more recent stressors are risk factors, precisely how these environmental influences interact with genetic vulnerability remains obscure. In recent years, considerable advances have been made in beginning to understand the genetic substrates that underlie disease vulnerability, and the interaction of genes, early-life adversity, and the epigenome in influencing gene expression is now being intensively studied. The role of inflammation and other immune system dysfunction in the pathogenesis of major depression is also being intensively investigated. Brain imaging studies have provided a firmer understanding of the circuitry involved in major depression, providing potential new therapeutic targets. Despite a broad armamentarium for major depression, including antidepressants, evidence-based psychotherapies, nonpharmacological somatic treatments, and a host of augmentation strategies, a sizable percentage of patients remain nonresponsive or poorly responsive to available treatments. Investigational agents with novel mechanisms of action are under active study. Personalized medicine in psychiatry provides the hope of escape from the current standard trial-and-error approach to treatment, moving to a more refined method that augurs a new era for patients and clinicians alike.

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> "Depression is the most unpleasant thing I have ever experienced…. It is that absence of being able to envisage that you will ever be cheerful again. The absence of hope. That very deadened feeling, which is so very different from feeling sad. Sad hurts but it's a healthy feeling. It's a necessary thing to feel. Depression is very different."
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> —J.K. Rowling, interview, London *Times*, 2000

The well-known parable of the blind men and the elephant is the story of blind men who have never come across an elephant, and as each feels a different part of the elephant's body, they describe the elephant based on their limited experience. None, of course, captures the totality of the animal. So it is with depression. There have been hundreds of volumes and many thousands of reports on various aspects of depression, ranging from nosology and epidemiology to pathophysiology and treatment. Each of these disciplines, applying, among other things, genetics, brain imaging, immunology, neurotransmitters and second messengers, neurotrophic factors, and animal models, like the blind men, "sees" parts of depression. Yet in spite of these efforts, our understanding of this major psychiatric disorder and its treatment remains limited.

Because so much has been published on the etiology and treatment of depression and yet there is so much that we do not know, I focus in this overview of the field on novel findings in all of the subdisciplines that comprise psychiatric investigation. By its very nature, this review cannot be comprehensive; rather, the major goal here is to provide an overview of where we are and where we need to go in order to attain our ultimate goals: an understanding of the pathogenesis of depression, which in turn will enhance our understanding of which of the many currently available evidence-based treatments will be most safe and effective in a given patient and aid us in the development of more effective treatments. What is most striking is the remarkable

lack of concordance among researchers and clinicians on almost every single one of the major areas in the depression field. Indeed, there remains controversy about the appropriate approach and interpretation of the extant data regarding diagnosis, genomics, gene-by-environment interactions, animal models, mechanisms of action of evidence-based treatments, prediction of antidepressant efficacy and side effects (personalized medicine), efficacy and side effect burden of currently available treatments, and development of novel treatments. Perhaps this is not that different from other medical fields, such as oncology, neurology, and infectious disease, and it would appear to be similar to controversies in the posttraumatic stress disorder and schizophrenia fields.

THE BASICS

Depression was recognized by Hippocrates (ca. 460–377 B.C.), Galen (ca. 129–199 A.D.), and Ishaq Ibn Imran (10th century A.D.), and these physicians' early clinical descriptions well mirror those of today, including a profound loss of the capacity to feel pleasure, severe dysphoria (despondency), and a loss of will (1). These symptoms are similar to those of severe bereavement but occur in the absence of any clear precipitating event. Major depressive disorder is the focus of this discussion, and because of space constraints, there will be no coverage of bipolar depression, depression during pregnancy or the postpartum period, or childhood depression. The DSM-5 criteria (2), similar but not identical to those of ICD-10 (3), require the presence of five of nine well-known symptoms, including depressed mood, loss of pleasure or interest, significant appetite disturbance or body weight change, sleep disturbance, loss of energy, psychomotor changes, excessive guilt and/or worthlessness, decreased concentration, and recurring thoughts of death and/or suicide. Some common symptoms of major depression, such as diurnal mood variation and unexplained crying spells, are not included in the current diagnostic criteria. Further descriptors of major depression include levels of severity (mild, moderate, or severe) and certain features (psychotic or atypical features, seasonal pattern, melancholia). To be clear, unlike in other branches of medicine, this categorical or syndromal diagnosis of major depressive disorder rests entirely on descriptive phenomenology. Unlike the diagnosis and management of diabetes, which utilize HbA_{1C} levels, fasting blood glucose levels, and other metrics, the diagnosis of major depressive disorder has no validated biological markers that can serve as a validated ancillary diagnostic tool. Thus, unlike the use of EEG to document and augment clinical observations and patient history in the management of epilepsy, major depressive disorder relies entirely on patient self-report and clinician observation. Because epidemiology, clinical research, and clinical service delivery depend on this classification, and because two patients can meet criteria for major depressive disorder and have virtually no overlap in symptoms—for example, hypersomnia versus insomnia, decreased appetite versus increased appetite, suicidal ideation versus no suicidal ideation, and so on—the end result is a remarkable degree of heterogeneity in the diagnosis of major depressive disorder, an issue that has plagued the field. One group actually reported that some 1,500 DSM-IV symptom combinations can fulfill the diagnostic criteria for major depressive disorder! (4) It is clear that an 85-year-old patient with no prior history or family history of major depression who presents with many of the cardinal features of major depression is very different from a 30-year-old patient with a positive family history who presents with similar symptoms. This heterogeneity in the diagnosis of major depressive disorder is discussed further below in the context of research results in genomics, brain imaging, and treatment studies. Moreover, as others have pointed out (5), the low degree of reliability of the diagnosis of major depressive disorder in the DSM-5 field studies is a major concern, especially if all of the biological marker studies described below depend on this "gold standard."

Several large-scale epidemiological studies using the DSM and ICD diagnostic classifications have revealed major depression to be remarkably common, as exemplified in the National Comorbidity Study Replication sample, with a 12-month prevalence rate of 6.6% and a lifetime prevalence rate of 16.2% (6). Similarly, data from the World Health Organization cite 12-month prevalence rates of 5.5%−5.9% and lifetime prevalence rates of 11.1%−14.6% (7). The average age at onset is 25 years. Women are twice as likely to suffer with depression, and the factors that contribute to this vulnerability remain obscure.

Another major source of disagreement in the field is how to deal with the substantial psychiatric comorbidity associated with the diagnosis of major depressive disorder. This includes both syndromal comorbidity and the presence of a variety of other psychiatric symptoms in patients with major depression. Indeed, comorbidity is more the rule than the exception, and this relationship is bidirectional. For example, the rate of major depression in patients with posttraumatic stress disorder (PTSD) is quite high, and a substantial proportion of patients with PTSD, particularly those with a history of early-life trauma, meet criteria for major depressive disorder (8). There are remarkably high levels of comorbidity of major depression in patients with syndromal anxiety disorders, such as social anxiety disorder and panic disorder—and indeed, prior to the development of DSM-5, an entire meeting was dedicated to determining whether generalized anxiety disorder exists as a freestanding diagnostic entity or is simply the *forme fruste* for major depression (9). The decision was made, based on the available evidence, to retain generalized anxiety disorder as a discrete diagnosis, but the controversy continues. Patients with obsessive-compulsive disorder (OCD) and substance use disorders also exhibit high prevalence rates of major depression. These comorbidities raise serious questions about the conduct of depression research. Should patients with comorbid psychiatric disorders be included in clinical studies of major depression, either pathophysiological or therapeutic? Because eliminating such patients to obtain a "pure" clinical

sample of major depression effectively excludes a large proportion of the patients in clinical practice, any results obtained cannot be generalized to the overall depressed patient population.

Another important consideration is the course of major depression, which can be quite variable, ranging from patients who receive no treatment and spontaneously recover to those who develop chronic depression. What is clear is that for the majority of patients, recurrence rates are high, especially in the absence of continued treatment.

Finally, the age-old question of nature versus nurture in the etiology of major depression must be taken into account. As discussed below, it is now clear that a substantial risk for vulnerability to major depression is genetic, in the range of 35%−40% (10). The remainder of the risk is environmental, which includes a host of factors, including a history of childhood maltreatment, substance and alcohol abuse, more recent life stressors, social isolation, air pollution, socioeconomic status, and educational attainment (11–13). How these factors interact with genetic vulnerability to raise or lower the threshold for developing an episode of major depression is of great interest.

MEDICAL COMORBIDITY

It has long been known that patients with certain common medical disorders exhibit rates of major depression that far exceed that of the general population. The prototype is, of course, patients with primary hypothyroidism: such patients are known to be nonresponsive to antidepressants and often show a return to euthymia with adequate thyroid hormone replacement or, if not, once euthyroid, do respond to antidepressant treatment (14). In addition, it is now clear that there is a bidirectional relationship between the hypothalamic-pituitary-thyroid axis and major depression, with patients with major depression exhibiting higher than expected rates of thyroid disease, most prominently symptomless autoimmune thyroiditis, as evidenced by the presence of antithyroid antibodies (15). There is now evidence that patients with major depression who have "high-normal" thyroid-stimulating hormone levels actually significantly benefit from thyroid hormone supplementation to achieve euthymia (16).

However, a host of other medical disorders present with inordinately high rates of comorbid major depression; these include certain cancers (even before diagnosis, most exemplified by pancreatic cancer); cardiovascular disease and stroke; diabetes; and, as demonstrated more recently, several autoimmune and inflammatory disorders, other CNS disorders such as multiple sclerosis, Parkinson's disease, and Huntington's disease, and chronic obstructive pulmonary disease (17–20). Recently, a common and understudied condition, burning mouth syndrome, a chronic oral pain disorder characterized by a generalized or localized burning sensation without the presence of any mucosal lesions, was found to be associated with high rates of major depression (21). A number of studies have documented the relatively poor treatment response in depressed patients with comorbid medical disorders, particularly in the elderly (22). It is important to note that several years ago, Schatzberg and his colleagues documented the high rate of pain symptoms in patients with major depression (23), and some have suggested that pain be added to the diagnostic criteria for major depressive disorder. The prominent comorbidity of major medical disorders, coupled with suicide, is the primary cause of the well-documented premature mortality in patients with major depression. Indeed, patients with depression die an average of 8 years earlier than comparable persons without depression (24). The underlying pathophysiological basis for the relationship between these major medical disorders and major depression remains largely obscure and understudied. There is some suggestion that inflammation may be one mechanism by which depression is associated with increased vulnerability to several of these disorders (see the section below on inflammation). Thus, it has been suggested that depression is a systemic illness that affects the brain and the body, with the latter effects associated with increased vulnerability to, and poor prognosis of, a number of medical disorders.

ANIMAL MODELS OF DEPRESSION

Similar to many of the other areas discussed in this review, this topic is also fraught with controversy. Let's start with consideration of the fact that depression is a uniquely human condition. It simply does not occur in any other species. Although various animals, particularly nonhuman primates, are capable of exhibiting symptoms similar to depression in response to loss or if exposed to severe levels of stress, how these responses relate to the subjective experience of human depression is unclear. While animals in their natural habitat have been observed to exhibit some of the features of depression, the longitudinal nature of depression, including its recurrent course, is not apparent in animals. Similar to the relatively extreme measures necessary to induce rodents to consume alcohol, animal models of depression in rats or mice most often involve exposure to various types of stressors, including restraint stress, social isolation, electric foot shock, learned helplessness, chronic social defeat, olfactory bulbectomy, maternal deprivation, or chronic unpredictable stress (25). Such perturbations are out of the ordinary in the naturally occurring experiences of rodents in the wild. The results observed in such paradigms include a decrease in appetite, sexual behavior, and locomotor activity and an increase in assessed anxiety. Several of the cardinal features of major depression are impossible or virtually impossible to assess in rodents, including suicidality, decreased concentration, overwhelming guilt, and self-reproach. In addition to the models described above are pharmacological models used to induce depression, for example, the use of chronic corticosterone administration or serotonin depletion and genetic models that have bred generations of rodents for depressive symptoms (26–28). Another drawback of these models is that

most of them have been limited to male rodents, a concern in view of the greater propensity for women to develop major depression. In spite of the clear differences between the syndrome of major depression and the phenotype of these animal models, a number of the models have face validity in predicting antidepressant activity of known and putative antidepressants. This has been both a curse and a blessing in that it has resulted in somewhat of a self-fulfilling prophecy; thus, if imipramine is effective in these models, new agents that test positive may well be "imipramine-like" and may therefore lead to the categorization of potentially useful new antidepressants that screen negative in these tests as being of no further interest.

One interesting novel approach has been the administration of exosomes from depressed patients to laboratory mice (29). Exosomes are small vesicles 40–100 nm in size that are released by many cell types, including neurons and glia. They contain a variety of molecules, including DNA, mRNA, and microRNA as well as proteins. One report (29) documented a microRNA, hsa-miR-139-5p, that is expressed differentially in exosomes of depressed patients compared with control subjects. When exosomes from these depressed patients were injected into normal mice, depressive-like behaviors were observed in several standard mouse depression models, including the forced swim test, tail suspension, and novelty-suppressed feeding. Moreover, treatment with exosomes from healthy control subjects or an antagonist of miR-139-5p blocked the depressogenic effects of the exosomes from depression patients in mice.

GENETICS, EPIGENETICS, AND GENE-ENVIRONMENT INTERACTIONS

This is a large literature, and I will only briefly discuss the major issues in the field. The seminal question remains that of understanding the discrepancy between the clear findings that approximately one-third of the risk for major depression is genetic and the absence of identification of the genetic substrates that mediate this risk. Genome-wide association studies (GWASs) have attempted, in relatively large samples, to identify the loci that confer risk for major depression. The results have largely been disappointing on two counts. First, in early studies, there appeared to be overlap in risk for major depression and both bipolar disorder and schizophrenia (30). Second, each of the gene variants (single-nucleotide polymorphisms [SNPs]) identified, although statistically significant because of the large number of subjects studied, alone exerts a very small effect in terms of vulnerability to major depression. Third, unlike schizophrenia and autism spectrum disorder, the identification of copy number variants or rare variants of large effect by exome sequencing in major depression has not been as robust as expected (31).

Although the early GWAS studies failed to detect any meaningful and specific depression-associated loci (32), more recent studies have been more successful. Howard and colleagues (33) meta-analyzed data on more than 807,553 individuals (246,363 case subjects and 561,190 control subjects) from three of the largest depression GWASs. They identified 102 independent variants, 269 genes, and 15 gene sets associated with depression, including some previously reported to be involved in synaptic structure and neurotransmission. A replication sample of more than 1.3 million individuals from 23andMe confirmed 87 of the 102 depression-associated variants. However, in that study there was again evidence of shared genetic components between depression and other psychiatric disorders, including anorexia nervosa, attention deficit hyperactivity disorder, schizophrenia, and bipolar disorder.

A breakthrough was clearly the identification of two loci for major depression in a study of 5,303 Han Chinese women with recurrent major depression and 5,337 control subjects (34). Prior to that study, there were no robustly replicated genetic loci identified in more than 9,000 study subjects. What was unique about this study was the selection of only women who had recurrent and severe major depression, a design that reduced phenotypic heterogeneity in an ethnically homogeneous population. The two genome-wide loci identified that conferred risk for major depression were both on chromosome 10, one near the Sirtulin 1 gene (SIRTI) and the other in an intron of the phosphorlysine phosphohistidine inorganic pyrophosphate phosphatase gene (LHPP). Further analysis of 4,509 cases of the most severe subtype of major depression, melancholia, yielded an increased genetic signal at the SIRTI locus. The success of this study was likely driven by several factors—the rigid inclusion criteria for major depressive disorder (recurrent cases only and exclusion of mild depression), study of women only, and limitation to an ethnically homogeneous population. This study and others raised a seminal question that has plagued the depression field in general and the depression genetics field in particular, namely, the use of minimal versus in-depth phenotyping. To state the two extremes, minimal phenotyping would be exemplified by the use of patient inclusion in the depression group as defined by the use of the term "depression" or the prescription of an antidepressant in an electronic medical record or in self-reports. In-depth phenotyping, which is by its very nature much more labor- and cost-intensive, would utilize categorical and dimensional measures to determine syndromal status and symptom severity (as well as comorbidity), such as the Structured Clinical Interview for DSM-5 or the Mini International Neuropsychiatric Interview for the former and any one of the many depression symptom severity scales, such as the Hamilton Depression Rating Scale (HAM-D) or the Montgomery-Åsberg Depression Rating Scale (MADRS) for the latter. Cai et al. (35) addressed this issue by comparing minimal phenotyping and strictly defined major depression in a GWAS. The genetic architecture of minimal phenotyping definitions of depression was clearly different from that of strictly defined major depression, the former enriched for nonspecific effects. The heritabilities of major depression defined by minimal phenotyping strategies were much lower than those of major depression defined by full

DSM-5 criteria. Most importantly, a larger percentage of the genome contributes to the shared genetic liability between minimal phenotyping definitions of depression and other psychiatric conditions than between strictly defined major depression and other conditions. It is my hope that these data will finally put an end to the notion that moving away from strict phenotypic characterization of major depression could find utility in elucidating the biological basis of depression, including its genetic underpinnings. Surely, well-characterized patients with well-defined subtypes, such as atypical, psychotic, and melancholic, will help elucidate the pathophysiological differences among them.

Several future directions are evident from these and related findings, and many have recently been summarized (36). GWAS identifies genomic regions, not the underlying biological mechanisms. Because the effect sizes for each of the identified variants is small, care must be taken to pursue any individual locus, in view of the costs and difficulties in conducting functional studies. As noted above, the role of rare versus common variants has not been fully explored in major depression.

The seesaw of opinion related to gene-by-environment interaction studies and their utility in elucidating the pathogenesis of major depression has been confusing to the field. After a slew of single gene candidate studies were reported and subsequently not replicated in GWASs, they fell into disfavor. Of course, many of these "replications" suffered from the phenotyping quality issue described above as well as from relatively small sample sizes. These candidate gene studies were largely based on our understanding of the hypothesized underlying biology—for example, the corticotropin-releasing hormone (CRH receptor 1 [CRHR1]) polymorphism interaction with a history of child abuse and neglect appearing to result in increased vulnerability to major depression (37). I would suggest that such an approach is complementary to the polygenic risk score (PRS), which has largely supplanted it. I view this as a particularly important avenue of investigation because the GWAS findings explain only a small fraction of the heritability of major depression. I would suggest that this gap will be filled by understanding gene-by-environment interactions and the role of epigenetic mechanisms. I find it particularly interesting, in relation to depression, that gene-by-gene (epistasis) and gene-by-gene-by-environment interactions have been relatively ignored, although our group demonstrated the utility of the latter approach (38). In addition, others have suggested that neither individual GWASs nor meta-analytic combinations have been helpful in disclosing which genetic variants contribute to a particular phenotype, and therefore most of the missing heritability is latent in GWAS data, which may conceal intermediary phenotypes. The PGMRA web server for phenotype-genotype interactions and causal relations introduces the concept of phenomics, which could be applied to major depression (39). In the end, of course, what is likely of paramount importance is the effect of genomic variation and epigenetic mechanisms on gene expression, and ultimately effects on the expression of proteins. DNA methylation is one form of epigenetic regulation, and although not as advanced as the GWAS investigations, scrutiny of the methylome has now been undertaken in major depression. For example, Aberg et al. (40) recently published the first large-scale methylome-wide association study (MWAS) of 1,132 individuals with major depression and control subjects and 61 postmortem samples of Brodmann's area (BA) 10 and in two postmortem replication samples (BA 10 and 25). Like GWAS results, this MWAS identified many depression-associated methylated CpGs with modest effects. Moreover, there was significant overlap in the depression-associated sites observed in blood and postmortem brain tissue. Of considerable interest is the recent report from the same group (41) in which blood samples from 581 patients with major depression were obtained at baseline for MWAS, and the results predicted future disease status 6 years later—that is, the presence or absence of a DSM-IV diagnosis of major depressive disorder—by calculating a methylation risk score, analogous to the PRS. The loci identified in the major depression sample overlapped with genes found in prior GWASs and included genes implicated in inflammation and autoimmune disease.

What has not been carefully scrutinized until recently is the interaction between critical environmental factors with genotype on DNA methylation. Recently Czamara et al. (unpublished data, January 2020) studied five independent cohorts totaling 1,074 individuals to determine the effects of child abuse and genotype on the methylome. Gene-by-child abuse interactions explained most variance in 80% of the DNA methylation sites, mapping to genes enriched in brain transcripts related to development and synaptic function. This underscores the importance of including genotyping in studies seeking to determine the effects of environmental factors on epigenetic marks.

Finally, a novel approach by Turecki's group (42) is noteworthy. This group recently reported the results of a single-nucleus transcriptomics study in the dorsolateral prefrontal cortex of 17 male individuals with major depression and 17 matched control subjects. More than 80,000 nuclei were sampled and 26 cellular clusters were identified, and >60% showed differential gene expression between the groups. The largest effects were observed in deep-layer excitatory neurons and oligodendrocyte precursor cells. Such an approach allows for the identification of cell-specific gene dysregulation in major depression, a major advance over previous studies of postmortem brain homogenates.

We are surely in our infancy in understanding the relative roles of these genetic and epigenetic alterations on relevant molecular mechanisms that involve the synthesis of critical proteins, including receptors, transporters, and enzymes.

THE PREEMINENT ROLE OF CHILD ABUSE AND NEGLECT

In a sea of controversy and discordant findings, it is quite clear that there is almost universal agreement that childhood

maltreatment, in the form of physical, sexual, and emotional abuse and neglect, is associated with a marked increase in risk for major depression (43). This finding has been replicated in a multitude of studies, and the data have been reviewed, including in large meta-analyses (44). Indeed, in many ways the emerging importance of early-life trauma in the pathophysiology of major depression has become the prototype for gene-by-environment interaction studies. For example, Peyrot et al. (45) conducted a study of 1,645 patients with major depression and 340 control subjects and determined that PRSs and childhood trauma independently affected major depression risk, but the effect of PRSs on depression was significantly increased in the presence of childhood trauma. Thus, patients with high PRSs and exposure to early-life trauma are at a particularly high risk for developing major depression. Moreover, it is now clear that patients with major depression with a history of early-life adversity exhibit a more virulent course of illness, including an earlier age at onset, more inpatient hospitalizations, more frequent suicide attempts and completed suicides, and relative resistance to evidence-based treatments, both psychopharmacology and psychotherapy (46). For example, in a recent study in France, Yrondi et al. (47) studied 256 patients with major depression and reported that there was a significant correlation between Childhood Trauma Questionnaire total score and MADRS and Quick Inventory of Depressive Symptomatology depression severity scores. More specifically, subscales of childhood sexual abuse and physical abuse were correlated with depression severity.

Although space constraints preclude a comprehensive discussion of this area, there is now a wealth of data on the manifold effects of childhood maltreatment on the CNS and on multiple physiological systems. In short, both laboratory animal studies and clinical studies have revealed long-lasting, persistent consequences of early-life adversity, including alterations in structural and functional brain imaging (48), immune function and inflammation, neuroendocrine axes, and the autonomic nervous system, to name just some of the findings (49). These profound effects are believed to mediate the shortened lifespan and increased vulnerability of victims of child abuse and neglect to a multitude of psychiatric and medical disorders, including major depression. However, these findings have other important implications. It is now unclear whether many of the biological alterations previously reported to occur in major depression are in fact actually a consequence of childhood maltreatment. This may be the case, for example, for the many reports of hypothalamic-pituitary-adrenal axis alterations in major depression, as well as the reports of reductions in the size of the hippocampus as assessed by structural MRI (50, 51). Unfortunately, in the vast majority of studies that have sought to uncover biological alterations in major depression, assessment of childhood trauma was not included. Future studies, both of pathophysiology and treatment, will need to consider assessment of early-life adversity because of both its profound effects on a number of putative biomarkers and its negative effects on treatment response.

WHAT HAPPENED TO THE MONOAMINE THEORY OF DEPRESSION?

If I were writing this review 20 years ago, I would have related a tidy story about how three monoamine systems in the brain—serotonin, norepinephrine, and dopamine—are the major players in the pathophysiology of depression. The narrative would go something like this: Serotonin and norepinephrine circuits arise in the most ancient parts of the brain, in the raphe nuclei and the pons, respectively, and send widespread projections to the forebrain, where they exert control over a wide variety of physiological functions, many of which are awry in major depression, including appetite, libido, concentration, and mood. In addition, dopamine mediates the primary, perhaps pathognomonic, symptom of depression, namely, anhedonia. Depletion of these monoamines in laboratory animals with drugs such as reserpine or more selective agents that destroy serotonin or norepinephrine neurons leads to depressive-like symptoms in animals. Hundreds of published reports documented relative reductions of these neurotransmitters or their metabolites in CSF, blood, or urine of patients with major depression, and postmortem studies often supported these findings (52). Effective antidepressants were shown to act primarily on these circuits as reuptake inhibitors, thereby increasing the availability of these neurotransmitters in the synapse to further stimulate postsynaptic receptors. These observations, coupled with results of both depletion and provocative clinical studies such as the blunted growth hormone response to adrenergic and dopaminergic agonists in patients with major depression, supported these views (53). In those years, clinicians discussed patient symptoms as being a picture of a "dopaminergic" depression, with severe anhedonia and psychomotor retardation, or a "serotonergic" depression, with sleep disturbance and reduced libido.

Unfortunately, the monoamine theory as described has not stood up to close scrutiny. For example, reserpine, which depletes the brain of 95% of serotonin, dopamine, and norepinephrine, produces depression in only about 15% of subjects. If monoamines are that important in mood regulation, how can one walk around with <5% of one's monoamines and be euthymic? Second, the pharmacological effects of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) as antagonists at the monoamine transporter sites are immediate, yet their antidepressant effects are delayed for 3–5 weeks, and even longer in some patients. Third, reappraisal of the biochemical marker studies noted above identified many negative studies that revealed no alterations in indices of activity of these monoamine circuits in depressed patients. Fourth, some antidepressants clearly do not act as reuptake inhibitors at these sites, including bupropion, agomelatine, ketamine, pimavanserin, and others. Fifth, even in previously untreated patients with major depression, SSRIs and SNRIs achieve remission in no more than 50% of the population. Sixth, recent studies by our group (54) have revealed no

relationship between serotonin and norepinephrine transporter occupancy and treatment response in previously untreated patients with major depression who received escitalopram or duloxetine.

In spite of these "holes" in the monoamine theory, recent findings continue to implicate these systems in the pathophysiology of major depression. For example, in confirmation of a series of previous findings by Meyer and colleagues (55), Pizzagalli et al. (56) recently reported a reduction in dopamine transporter binding sites in 25 medication-free patients with major depression compared with 23 healthy control subjects, and these observations were confirmed in a postmortem study of 15 patients with major depression and 14 control subjects.

Another important and now repeatedly confirmed observation has been the increase in monoamine oxidase (MAO) B activity in the brains of patients with major depression, as assessed by positron emission tomography (PET). Moriguchi et al. (57) recently reported on 20 medication-free patients with major depression and 20 age-matched control subjects using a novel radioligand ([^{11}C]SL25.1188) to assess MAO-B activity. There was a marked increase in MAO-B activity in the patient group; 50% of the patients had MAO-B activity values in the prefrontal cortex higher than the highest levels in the control group.

In addition, there are many ongoing molecular pharmacology studies to determine the mechanism of action of antidepressants, going far beyond the monoamine transporter effects of these compounds. New studies have implicated the dopamine D_1 receptor (58) and the serotonin 5-HT_{5A} receptor (59), to name just two.

BRAIN IMAGING STUDIES

At first glance, brain imaging studies would appear to be ideal to elucidate the pathophysiology of major depression. Structural and functional MRI, the latter with all its subdisciplines and related methodologies (e.g., diffusion tensor imaging), as well as MR spectroscopy and PET, have all been applied to the study of major depression. Indeed, as recounted recently by Spellman and Liston (60), more than 2,300 publications are now available in this area. The important question to ask, of course, is how to interpret the results of such studies. As regards the many reports of structural (volumetric) alterations in one or another CNS structure in patients with major depression, I would offer the following considerations. First, the effects are generally quite small. Second, meta-analyses have largely not provided widespread support for many of these findings. Third, and perhaps most important, what does a volumetric change in, for example, the hippocampus or prefrontal cortex actually mean? Is this due to a change in brain water? Dendritic or axonal atrophy? Neuronal degeneration? Ratio of glia to neurons? Cytoskeletal changes? No postmortem studies that I am aware of have correlated structural MRI findings with histopathology to address these questions.

In terms of functional brain imaging, largely fMRI studies, the literature is enormous and could not possibly be reviewed here. However, I must quote my colleague Daniel Weinberger, who, in cautioning on the interpretation of fMRI studies, said, "Have you ever read any published fMRI study of any psychiatric disorder that had no finding?" A number of caveats must be taken into account in critically reviewing these studies. First, in relation to resting-state fMRI, is the question of what the "resting state" represents. For anyone who has ever been in an MRI scanner, the "resting state" is hardly resting. Subjects are lying in the scanner thinking about a range of topics—their children, their job, when this will be over, etc. Despite this concern, leaders in the field such as Mayberg, Schatzberg, Liston (61–63), and others provided a solid framework by identifying increased functional connectivity in the subgenual anterior cingulate, thalamus, and default mode network, decreased functional connectivity in frontoparietal task control networks, and alterations in frontoparietal control and default mode networks in major depression. These findings, as reviewed by Spellman and Liston (60), have been replicated in meta-analyses (64). Most of these studies are cross-sectional in nature, but they represent a beginning framework for further study. They also offer the opportunity to serve as a target of novel therapeutic interventions (see below). It is important to determine whether the brain imaging observations described above are due wholly to the diagnosis of major depression or in part by—or with contributions from—a history of childhood maltreatment. As noted above, there is already considerable evidence that the previously reported reduction in hippocampal size in major depression is in fact due entirely to childhood maltreatment and is unrelated to the syndromal diagnosis of depression (50, 51).

Another potential strength of brain imaging studies is the possibility of teasing out particular circuits that mediate specific depressive symptoms. One such recent example is the study by Rappaport et al. (65) in depressed adolescents in which a very discrete and incisive question was addressed, namely, What is the nature of reward circuitry in adolescence as a function of current and cumulative depression? The researchers found that current depression severity was associated with nucleus accumbens hypoactivity in response to the anticipation of a reward, whereas cumulative depression was associated with a blunted response to anticipation of reward in a cortico-striatal circuit. Such studies help to further refine our understanding of anhedonia in patients with major depression and provide a neuroanatomical basis for novel treatments.

In addition to providing the neurobiological basis for development of novel treatments such as deep brain stimulation, focused ultrasound, and novel forms of transcranial magnetic stimulation (see below), the major contribution of brain imaging studies may well lie in its serving as a component of the algorithm of personalized medicine in psychiatry to predict optimal response in an individual patient (see below).

THE IMMUNE SYSTEM AND INFLAMMATION

Nearly 20 years ago, my colleagues Dominique Musselman and Andrew Miller led a study in which we reported that depressed patients and depressed patients with various cancers, but not cancer patients without depression or healthy control subjects, exhibited increased plasma concentrations of interleukin-6 (IL-6), a proinflammatory cytokine (66). We were following up on the pioneering studies by Maes and colleagues (67), who reported increases in inflammatory markers in depressed patients, as well as studies by Kronfol (68) and Schleifer et al. (69), who reported alterations in various immune measures in depressed patients, as well as our own studies of high rates of autoimmune thyroiditis in patients with major depression (15). An entire field of psychoimmunology has blossomed in the past two decades. In the space below, I attempt to summarize the major findings. I refer to recent reviews for comprehensive coverage, including one of our own (70). Alterations in both the adaptive and innate immune systems occur in major depression. It is now clear that major depression is associated with systemic immune activation, comprising alterations in inflammatory markers, immune cell numbers, and antibody titers. Multiple meta-analyses have confirmed the findings that proinflammatory cytokines and acute-phase proteins are increased in patients with major depression; the strongest evidence is for IL-6, tumor necrosis factor (TNF), and C-reactive protein (CRP). There is also evidence for an increase in inflammatory cytokine gene expression in peripheral blood mononuclear cells in major depression. However, not all patients with major depression exhibit this profile, and more recent studies have attempted to clinically characterize patients with major depression with this profile. There are now multiple reports of marked increases in inflammatory cytokine concentrations in blood and CSF in patients with prominent suicidality (71). It is important to note that elevations in inflammatory cytokines have also been reported in other major psychiatric disorders, including schizophrenia and bipolar disorder (72). Along with this consistent finding of an increase in inflammatory markers in major depression is the equally compelling but seemingly discordant finding that patients with major depression are relatively immunocompromised, as evidenced by a decreased lymphoproliferative response of T cells, decreased natural killer cell activity, and a decreased number of T helper cells. In our study of inflammatory markers (73), we found that never-treated patients with major depression exhibited increased cytokine production. In addition, exposure of plasma from the patients with major depression to peripheral blood mononuclear cells from healthy volunteers resulted in immunosuppression. It is important to note that in the large GWAS studies cited above, an inordinate number of the major depression loci identified were related to immune function, and these data have been recently reviewed (74). Lago et al. (75), in a study of 485 patients with major depression and 625 control subjects, discovered a SNP on the gene for the human CD300f immune receptor that alters its signaling and is associated with protection against major depression in women.

Of relevance is the question as to whether patients with major depression are more likely to be infected with bacteria or viruses when compared with the general population. There is considerable evidence that a past history of major depression is associated with an increased risk of infections, and this is generally interpreted to mean that patients with major depression are relatively immunosuppressed—and this in spite of the observed increase in proinflammatory cytokines. A related and relatively unexplored area is the relationship of major depression to autoimmune disease, alluded to earlier in this review. This bidirectional relationship is now well established. Patients with major depression have an increased risk of developing autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, autoimmune thyroiditis, multiple sclerosis, and irritable bowel syndrome, and patients with these disorders have high rates of major depression (76).

One of the major controversies that has plagued this field is the relative reliance on peripheral measures of inflammation, as opposed to measuring inflammation in the CNS, and the question of whether increased peripheral cytokines are in fact capable of producing CNS effects and playing a role in the pathogenesis of major depression. Recently Felger and colleagues (77) measured CRP and inflammatory cytokines in CSF and plasma from medication-free depressed patients. Their findings support the hypothesis that CRP is a peripheral biomarker that reflects both peripheral and central inflammation. In addition, several studies have now shown increases in both CSF and blood indices of inflammation in depressed patients, and, most importantly, PET ligands to measure inflammation in the CNS, such as expression of the translocator protein (TPSO), have provided concordant findings, although controversy continues as to what TPSO binding represents (microglial activation versus local myeloid cell or monocyte infiltration).

The evidence of CNS inflammation notwithstanding, there is considerable reason to believe that elevations in peripheral inflammatory cytokines exert effects on the CNS and may mediate depression associated with such states (78). It is important to note the many lines of evidence that support this view. First, peripheral cytokines can enter the CNS via the circumventricular organs in the brain, which contain fenestrated capillaries, unlike other regions protected by the blood-brain barrier. Second, there is evidence that cytokines can be transported across cerebral capillaries by a transport mechanism. Third, cytokines can bind to receptors on vagal afferents that project to the CNS. Fourth, treatment of human subjects or laboratory animals with alpha interferon (previously used to treat malignant melanoma and hepatitis C) results in a cytokine "storm" and a marked increase in depressive symptoms and suicidality. Finally (and discussed in more detail below, in the section on treatment), there is evidence that anti-inflammatory treatments, including TNF antagonists, which do not cross the blood-brain barrier, possess antidepressant properties, especially in patients with major depression with evidence of increased inflammation.

As in the discussion above on brain imaging, the role of childhood maltreatment in the inflammation observed in patients with major depression is of paramount consideration. There is much evidence, preclinical and clinical, that early-life trauma results in a long-lasting increase in proinflammatory cytokine secretion (79).

TREATMENTS, OLD AND NEW

Unlike other serious mental disorders, for which we have a limited armamentarium, there are a multitude of evidence-based treatments for depression. There is overwhelming evidence that compared with placebo, antidepressant medications are effective treatments. Beginning with the MAO inhibitors and the tricyclic antidepressants in the late 1950s and 1960s, followed by fluoxetine, approved by the U.S. Food and Drug Administration (FDA) in 1987, a slew of other SSRIs (sertraline, paroxetine, citalopram, escitalopram, fluvoxamine), SNRIs (including duloxetine and venlafaxine), and, finally, a number of other compounds (bupropion, nefazodone, trazodone, mirtazapine, vortioxetine, reboxetine, agomelatine) were introduced, providing clinicians with much to choose from for initial monotherapy. All of these and others have been shown to be superior to placebo in the treatment of major depression and are approved by the FDA or its European counterpart.

The good news is that there are many FDA-approved antidepressants. The bad news is that monotherapy, even optimized by dosage and duration, results in remission in only a minority of patients. This is exemplified in the now classic open-label STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial, in which, as assessed by the HAM-D, only 28% of patients achieved remission with up to 40 mg of citalopram (80). In our randomized double-blind study of never-treated patients with major depression (81), approximately 50% of patients achieved remission after treatment with escitalopram, duloxetine, or cognitive-behavior therapy (CBT).

There is some controversy in the field about whether one antidepressant is more efficacious than another. With the exception of a series of studies that suggested that tricyclic antidepressants, and clomipramine in particular, were more effective than SSRIs (82) and meta-analyses that suggested that the SNRI venlafaxine was more effective than SSRIs (83, 84), there is no compelling evidence that in groups of patients any one antidepressant has superior efficacy, and the FDA has never awarded status of greater efficacy to any single agent. As described below, considerable effort is currently being expended on attempting to identify biomarkers that will aid in the prediction of optimal treatment for patients with major depression—that is, which antidepressant will provide the best efficacy and side effect profile for the individual patient sitting in your office. Barring such a development, we are left with a trial-and-error approach.

The unmet needs in the treatment of major depression have led to two major research areas: the search for novel antidepressants that are not "me-too" drugs and the development of augmentation/combination strategies. I briefly describe some of the latest findings.

To some extent, the early development of MAO inhibitors and tricyclic antidepressants, followed by the SSRIs and SNRIs, bolstered the monoamine theories of major depression because, by one mechanism or another, they increased the synaptic availability of serotonin, norepinephrine, and/or dopamine. However, some of the follow-up agents had little direct effect on these systems. One such example is bupropion, which was suggested to be a norepinephrine and dopamine reuptake inhibitor, but the concentrations required to generate such effects were not attainable with standard clinical dosages (85), and its mechanism of action remains obscure. Similarly, other antidepressants, some not available in the United States, such as agomelatine and tianeptine, clearly do not act directly on monoamine neurons or their receptors, and others, such as nefazodone, mirtazapine, and mianserin, exert relatively weak effects.

These observations, coupled with the observations noted earlier that even SSRIs may not act primarily via these systems and the emergence of novel antidepressants that clearly have little or no effect on monoamine circuits, such as esketamine, raise fundamental questions as to the mechanism of action of antidepressants and the underlying pathophysiology of major depression.

In addition to antidepressants, evidence-based psychotherapies, most notably CBT and interpersonal psychotherapy, are clearly effective in the treatment of major depression (86, 87), and there is some evidence of the efficacy of more psychodynamically based psychotherapies (88). There remains controversy about the relative efficacy of psychotherapy and antidepressants, with some arguing that they are equal and others suggesting that antidepressants are more effective in more severe depression (89, 90).

In recent years, remarkable progress has been made in the development and optimization of somatic nonpharmacological treatments, including electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagal nerve stimulation (VNS), and deep brain stimulation (DBS), and a host of other modalities a bit further down the road in development, including direct current stimulation and focused ultrasound. I cannot possibly summarize this area and do it any justice. Suffice it to say that ECT is generally regarded as the most effective of all treatments, and there has never been a well-powered comparison of ECT with any antidepressant in major depression. ECT is not without its side effects, including short-term memory loss, but modifications in electrode placement have, to a considerable extent, reduced this troubling concern. ECT, VNS, and rTMS are all FDA-approved for the treatment of depression, and several ongoing studies and recent advances in the field are worth noting. First, in collaboration with the Centers for Medicare and Medicaid Services, a very large multisite 5-year study of the efficacy of VNS is being undertaken in severe treatment-resistant major depression. This study will answer a great many unanswered questions in the field and

hopefully will result in third-party reimbursement for this invasive but potentially life-saving intervention. Advances in rTMS have been rapid in recent years, especially with the eye-opening results reported by Williams and colleagues (91) on the remarkable efficacy of accelerated theta-burst intermittent TMS delivered for 10 minutes every hour over 10 hours for 5 days directed at the precisely targeted dorsolateral prefrontal cortex in patients with extremely refractory major depression. Although it was an open study and clearly one that will need to be replicated in a sham-controlled design, the observed remission rate of >90% is nothing short of remarkable.

I would be remiss if I omitted mention of DBS. Pioneered by Mayberg and colleagues, early positive studies (92) were followed by industry-sponsored programs that were less successful. There are many reasons for such contrasting results, which can be said of many major depression trials—patient heterogeneity, electrode placement, and other patient and investigator variables. What is so important about DBS is that it was a therapy solidly based on the neurobiology of the disorder, whether focused on the subgenual cingulate cortex or the medial forebrain bundle. It is very difficult to accrue a patient population of sufficient size to accurately test the efficacy of this treatment. It is my hope that the work in this area continues.

In view of the failure of monotherapy to achieve remission in the majority of patients with major depression, a number of augmentation and combination strategies have been applied. Again, the clinician has much to choose from in treating a so-called treatment nonresponder/nonremitter or partial responder. Some of the strategies are monoamine based and are derived from preclinical observations, such as the use of lithium augmentation, which was first shown in rodents to potentiate the action of tricyclic antidepressants on serotonergic neurotransmission (93). Others are less grounded in basic neuropharmacology but have been shown to be efficacious in converting nonresponders to responders or remitters. These include a host of atypical antipsychotics, such as olanzapine, quetiapine, aripiprazole, brexpiprazole, risperidone, and others, some FDA-approved for this purpose (94). Other agents have also been reported to be effective in this regard, including thyroid hormone (T_3), pimavanserin (a serotonin inverse agonist), pramipexole (a D_2/D_3 agonist), ketamine and esketamine, brexanolone, estrogen (in perimenopausal women), and an increasing number of psychedelic drugs, such as psilocybin (95–99). Then of course there are the combination therapies including SSRIs and other antidepressants, most notably bupropion, venlafaxine, or mirtazapine (100).

All of these strategies are backed by evidence that among patients with major depression who have failed to benefit from SSRI or SNRI monotherapy, some percentage will respond to augmentation or combination, but the effect sizes are relatively small. For example, in the placebo-controlled brexpiprazole augmentation trials, only about 25% of patients treated with brexpiprazole attained remission, compared with 10% with placebo (101). Frankly, none of the augmentation or combination therapies provide robust effects in patients who are nonresponsive or partially responsive to SSRIs or SNRIs, despite statistically significant results. Moreover, many of the augmentation strategies have significant side effects, ranging from the weight gain with certain atypical antipsychotics to the concerns of cost, drug abuse liability, and tachyphylaxis with esketamine (102). Of course, one should not omit the data related to the combination of antidepressants and evidence-based psychotherapy, for which our group and others have provided ample evidence (103), nor the combination of antidepressants and stimulation techniques such as TMS (104).

What is so puzzling about this admittedly confusing field is the wide range of pharmacological agents, with few properties in common, and some that would appear to be quite antagonistic, that have been reported to augment the action of antidepressants in partial responders. How we can reconcile, for example, the efficacy of atypical antipsychotics such as olanzapine, quetiapine, or risperidone, all of which are D_2/5-HT_2 antagonists, and the efficacy of pramipexole, a D_2/D_3 agonist? What do lithium, T_3, pramipexole, atypical antipsychotics, and pimavanserin have in common? As discussed in the next section, we unfortunately have little to guide us as to which augmentation or combination therapy to choose for a given patient. Moreover, we know enough about the effects of antidepressants and psychotherapy on various brain circuits at least to conclude that it is unlikely that they share a common mechanism of action. All of this, of course, highlights our fundamental ignorance of the pathophysiology of major depression.

Before moving on to discuss personalized medicine, it is important to note that the treatment of patients with major depression with comorbid disorders, including anxiety disorders and PTSD, is a remarkably unexplored area, at least partly because such patients are excluded from most industry-sponsored studies. Some data are, however, available. We recently reviewed the major depression–PTSD treatment literature (105), and although it is somewhat limited, there is evidence of efficacy of combination pharmacotherapy and psychotherapy, as well as ECT.

PERSONALIZED MEDICINE IN DEPRESSION TREATMENT

A number of the unmet needs described above in terms of diagnostic acuity and treatment response in major depression could readily be fulfilled by the maturation of personalized medicine in psychiatry. There are two fundamental components of personalized medicine: the identification of individuals who are at risk for a particular disorder and the identification of the most optimal treatment for individuals who suffer with the disorder. Personalized or precision medicine has emerged as an innovative approach for disease classification, research, and clinical practice. Fundamentally, this emerging field attempts to combine a number of unique characteristics of an individual patient, including their symptom complex, various biomarkers such as brain imaging,

genomics/epigenetics, neuroendocrine and inflammatory measures, and environmental variables and lifestyle, in order to predict disease susceptibility, assist in diagnosis, and select the most effective treatments, maximizing the likelihood of remission and minimizing adverse effects (106–108). This approach has been remarkably successful in oncology (109), and there is no reason why it should not be equally successful in psychiatry. Unlike oncology, which has cancer histopathology as the sine que non for diagnosis, we are plagued with highly complex, heterogeneous presentations within our syndromal diagnostic classifications, as exemplified in major depression. I would suggest that in view of this, it is unlikely that any single biomarker or approach will provide the basis for reliable prediction of individual treatment response. This is exemplified by the failure of commercially available pharmacogenomic tests to predict either antidepressant efficacy or side effects, in spite of the many claims to the contrary. This has been reviewed by the APA Work Group on Biomarkers and Novel Treatments (110) and others (111–113) who have come to the same conclusion. Indeed, the largest randomized clinical trial of pharmacogenomics to predict antidepressant efficacy, the Genomics Used to Improve Depression Decisions (GUIDED) study, failed to meet its primary endpoint, a change in HAM-D score, and remarkably also failed to predict side effects (114). Studies of these commercially available tests are in general burdened by small sample size, lack of blinding, unusually low remission rates, and, most importantly, the fact that the algorithm used by each company is proprietary and therefore not evaluable by journal reviewers or clinicians. For reasons that are unclear, perhaps related to intellectual property, many promising genetic variations, such as SNPs that are reported to predict antidepressant treatment response by our group and others, such as FKBP5, CRH binding protein, GPR56/ADGRG1, and NET (115–117), are not included in any of the commercially available tests. Indeed, the FDA has issued warnings about the lack of scientific evidence underlying these tests and the dangers for patients who discontinue antidepressants after receiving a warning about potential adverse effects of a medication they are currently receiving, with potentially disastrous outcomes associated with subsequent relapse (118). In spite of my concern about the currently available pharmacogenomic tests, I have little doubt that pharmacogenomics, coupled with a variety of other types of data, will play an important role in the future in prediction of antidepressant response.

In addition to pharmacogenomics, the other two major areas that have been explored as putative indices of treatment response in major depression are brain imaging and EEG. Space constraints preclude any serious review of the former area, but it is clear that functional connectivity studies, including those noted in an earlier section and others, such as that based on the 1,000-patient International Study to Predict Optimized Treatment in Depression (iSPOT-D) (119), hold great promise. As regards EEG, as recently as 2019, the APA Work Group on Biomarkers and Novel Treatments reviewed the literature and concluded that the available evidence did not support EEG as a reliable predictor of antidepressant use (120).

However, two recent reports lend support to the notion that more advanced analytic techniques applied to EEG data provide strong support for rethinking this conclusion. Wu et al. (121) studied 309 patients with major depression in the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression (EMBARC) study and identified predictions of sertraline response. This was confirmed in two replication samples. More recently, Zhdanov et al. (122), using a machine-learning approach in 122 patients treated with escitalopram, found that baseline EEG recordings identified the SSRI responders with accuracy of almost 80% (sensitivity and specificity of 67.3% and 91%, respectively). For those patients in whom EEG was obtained at week 2 of treatment, the prediction was even better.

A number of recent developments will all contribute to the eventual success of personalized medicine in psychiatry. These include the achievement of very-large-scale data collection, rendered easier by the often-criticized electronic medical record. The increasing use and availability of digital technology tools, especially wearables, which can collect objective and subjective data from patients, allow for multiple domains to be tracked continuously. Such measures can include heart rate and respiratory parameters, motor activity, and sleep architecture, to name a few. Such devices are being adopted in cardiology and endocrinology and will surely be incorporated into personalized medicine in psychiatry. The game-changer here is the development of machine learning, a form of artificial intelligence that is able to take hundreds, even thousands, of measures into a model that can predict outcomes. It has been used with great success in the financial sector, transportation, and social media and is now being applied in medicine. For example, machine learning has been applied with some success to the STAR*D phase I study and the Combining Medications to Enhance Depression Outcomes (COMED) study to identify remission with citalopram, escitalopram, and combined escitalopram-bupropion but not combined venlafaxine-mirtazapine (123). Similarly, machine-learning analysis of data from the Genome-Based Therapeutic Drugs for Depression (GENDEP) study resulted in prediction of response and remission to escitalopram and nortriptyline (124). What is now clearly emerging is the inclusion of multiple types of data, ranging from genomics to gene expression to early-life trauma to functional brain imaging, to enrich machine-learning models and come closer to real clinical utility. Already, reports are appearing in which inclusion of "multi-omics" coupled with other data, including metabolomics and other biomarkers, was found to significantly improve prediction accuracy for antidepressant treatment outcomes (125). Prediction of treatment response to CBT and other psychotherapies is also an active avenue of investigation, and it includes both genomics (126) and brain imaging approaches.

CONCLUSIONS

After a half century of research on the pathophysiology and treatment of major depression, it is remarkable how much we have learned and perhaps even more remarkable how much we do not know. Below I outline the major issues and unanswered questions.

1. The diagnosis of major depressive disorder remains fraught with difficulty because of the remarkable heterogeneity that is captured under this umbrella term. The definitions of response and remission are arbitrary, and serious questions remain about the utility of those measures. A HAM-D score of 7 or a MADRS score of 10 is not euthymia, in spite of these metrics currently being used to define remission. The definition of treatment-resistant depression is still not generally agreed upon, especially as regards how one defines an adequate treatment trial and the number of failed treatments that are required for such a classification. How to handle the common psychiatric comorbidities to major depression, such as PTSD, OCD, social anxiety disorder, and generalized anxiety disorder, in clinical research or practice remains unclear. Although the Research Domain Criteria approach proposed by the National Institutes of Mental Health (NIMH) seemed to hold promise, and it still may in research studies, as former NIMH director Thomas Insel noted, it has not changed clinical practice (127).
2. It is clear that only a minority of patients with major depression achieve remission with an adequate monotherapy trial. We must conclude, therefore, that our standard treatments remain suboptimal for many, and possibly most, patients. Augmentation strategies, of which there are many, are effective in some patients but also fraught with side effects (e.g., those associated with atypical antipsychotics and lithium).
3. The mechanism of action of antidepressants is unknown. In spite of intensive research in this area, none of the theories of antidepressant action have been substantiated, nor do they appear applicable to all antidepressants. This includes their action on monoamine circuits, neurogenesis, second messengers, or changes in gene expression. In addition, the mechanisms of action of ECT, TMS, and VNS as well as evidence-based psychotherapy remain obscure. Similarly, the mechanisms of action of the variety of augmentation strategies are equally elusive.
4. The holy grails of personalized medicine in depression, namely, the identification of those who are at risk for depression and the ability to choose the best and safest treatments for an individual patient, have not yet been achieved.
5. Much of the aforementioned shortcomings are secondary to our poor understanding of the pathophysiology of major depression. In spite of 40 years of research, with a multitude of "windows" into the brain, the fundamental etiology of major depression remains unknown. However, considerable advances have been made in genomics, epigenetics, inflammation, and environmental factors. Perhaps the brain has a limited repertoire of response to injury and major depression is a final common pathway—one that can be reached by multiple roads, as exemplified, for example, by major depression associated with hypothyroidism or hypogonadism.
6. The factors underlying the higher prevalence rates of major depression in women compared with men remain unknown.
7. Mechanistic studies of the high comorbidity rates of major depression and major medical disorders are sorely lacking. This is due in part to the fact that no National Institutes of Health component has taken ownership of this area, and therefore funding for this research is limited.

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