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Major Depressive Disorder

Review

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Depression describes both a transient mood state experienced by virtually all individuals at some time in their life as well as a clinical or biobehavioral syndrome, usually called Major Depressive Disorder (MDD). MDD is a medical condition that includes abnormalities of affect and mood, neurovegetative functions (such as appetite and sleep disturbances), cognition (such as inappropriate guilt and feelings of worthlessness), and psychomotor activity (such as agitation or retardation). It is one of the oldest, well-recognized medical disorders, having been clearly described in medical texts dating back to ancient Greece. When MDD occurs with an individual who has also had a history of episodes of mania, this is called Bipolar Disorder (previously termed Manic-Depressive Illness). In this review, we will be focusing on MDD when it occurs without a history of mania, where it is often called Unipolar Depressive Disorder.

Current diagnostic criteria for MDD (see for example the American Psychiatric Association's DSM-IV manual) represent a clinical and historical consensus about the most important symptoms and signs of depressive illness. However, affected individuals display quite a wide variation in clinical symptoms and signs. Furthermore, the current diagnostic conventions are, to some degree, arbitrary. Debate continues as to whether MDD is best conceptualized as a disease or as the extreme of a continuum of increasingly disturbed affective regulation.

This review outlines our current understanding of this common and frequently disabling disorder and explores the challenges we face in determining the genetic and neurobiological basis.

Epidemiology

Large-scale epidemiological studies have given us, for the first time, a detailed view about the current and lifetime prevalence of MDD. In what is probably the best of these studies in the United States (called the National Comorbidity Survey), the lifetime prevalence of MDD, as defined by the American Psychiatric Association's DSM-III-R criteria, was estimated at 17%. This same survey found that nearly 5% of the population reported meeting criteria for MDD in the last 30 days (Blazer et al., 1994). As has long been suspected, MDD is probably the most common of psychiatric disorders and, indeed, among the most common of major biomedical conditions in "first-world" countries such as the United States. Consensus, however, has not been reached about the single best estimate of population risk, as other studies have reported rates both substantially lower and somewhat higher than those reported in the National Comorbidity Survey. As is true in other areas of epidemiologic research, response patterns to interviews are sensitive to the specific wording of items, techniques used to motivate "effortful responding" and the organization of the assessment instrument.

The field of psychiatric epidemiology has identified a substantial list of putative risk factors for MDD. As in any nonexperimental subject, one difficulty has been to discriminate association from causation. Four risk factors stand out in the consistency of their association with MDD and the level of evidence suggesting that at least some of the association is indeed causal: gender, stressful life events, adverse childhood experiences, and certain personality traits. Across many studies, varying widely in time and place, women have been shown to be at consistently greater risk for MDD than men. In most studies, the ratio of prevalence rates in women to men has been in the range of 1.5 to 2.5. In the National Comorbidity Study, the lifetime prevalence of MDD in the US population was estimated to be 21.3% in women and 12.7% in men (Blazer et al., 1994). A wide range of environmental adversities such as job loss, marital difficulties, major health problems, and loss of close personal relationships are associated with a substantial increase in risk for the onset of MDD (Kessler, 1997). A range of difficulties in childhood including physical and sexual abuse, poor parent-child relationships, and parental discord and divorce almost certainly increase the risk for MDD later in life. Certain kinds of personality traits appear to predispose to MDD, with the best evidence available for the trait termed "Neuroticism." Neuroticism, first proposed by the British psychologist Eysenck, is a stable personality trait that reflects the predisposition to develop emotional upset under stress. A range of other risk factors has been proposed for MDD, although in general the evidence for the existence of a causal association is weaker. These would include low social class, urban residence, separated or divorced marital status, low levels of social support, and being in a more recently born age group. A recent WHO report (Murray and Lopez, 1996) ranked depression as the fourth medical condition with the greatest disease burden worldwide, measured in Disability-Adjusted Life Years, which express years of life lost to premature death and years lived with a disability of specified severity and duration. The same report predicted that depression would be the second condition with the greatest disease burden worldwide by 2020 (Murray and Lopez, 1996).

Course of Illness

MDD is not a disorder exclusively limited to adult and elderly populations. A substantial proportion of patients experience their first episodes of MDD during childhood

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and adolescence. In such occurrences of early-onset MDD, these individuals typically continue to suffer from episodes of MDD during adulthood as well. For most people, MDD is a life-long episodic disorder with multiple recurrences (averaging one episode in every 5-year period), with approximately 20%–25% of major depressive disorder patients experiencing a chronic, unremitting course (Mueller and Leon, 1996). The chronic and recurrent course of MDD is a major clinical issue, often requiring long-term prophylactic treatment.

Genetics

Most recent family studies have reported an approximately 3-fold increased risk for MDD in the first-degree relatives (parents, siblings, offspring) of individuals with MDD versus the general population, although there is some variation, due most likely to differences in diagnostic and sampling (proband) criteria (Sullivan et al., 2000). From family studies alone, however, it is not possible to determine how much of the resemblance for risk to MDD in relatives results from genetic factors versus family environment. MDD has been the subject of only three adoption studies, but well over a dozen twin studies. The results of the adoption studies have been surprisingly equivocal, with one study each showing no evidence, weak evidence, and strong evidence for the effect of genetic factors on risk to MDD (Sullivan et al., 2000). The results of twin studies of MDD have, by contrast, been both more robust and more consistent. We recently reviewed the results of the five twin studies of MDD that met rigorous methodological criteria (Sullivan et al., 2000). Of these five studies, three were based on community samples, one on a hospital sample, and one on both. Applying model-fitting jointly to all five of these studies, results did not differ significantly across studies and indicated that twin resemblance for the liability to MDD could probably be entirely explained by genetic factors, although a possible small influence for shared environmental factors could not be ruled out. The estimate of the heritability of liability to MDD in these studies was 33%, an estimate in the range of that found for many common and important biomedical traits such as blood pressure and serum cholesterol. Of the many other questions addressed in family, twin, and adoption studies of MDD, three are of particular interest. First, what is the relationship between unipolar MDD and bipolar affective illness? The two disorders have some familial relationship, as rates of MDD are elevated in relatives of bipolar patients. However, they are not the same condition. In monozygotic twins concordant for affective disorder, many more twins have the same form of illness (i.e., unipolar versus bipolar) than would be expected by chance. The most popular theory, supported by most but not all studies, suggests that the two disorders share an underlying disease liability, with bipolar disorder as the more severe or deviant form of illness (Tsuang and Faraone, 1990).

Second, can we distinguish on the basis of clinical history those individuals whose depressive illness is largely "genetic" versus "environmental"? The answer appears to be "at least partly." Affected individuals at high familial risk for MDD tend to have recurrent episodes, high levels of episode-related impairment, and perhaps an early age at onset (Kendler et al., 1999). Third, how do genes and environment combine to influence risk for MDD? Limited evidence suggests that genetic factors partially influence overall risk of illness but also influence the sensitivity of individuals to the depressogenic effects of environmental adversity (Kendler et al., 1995).

The techniques of genetic epidemiology infer the magnitude of genetic effects from the patterns of resemblance in relatives based on the simple but powerful laws of Mendel. With increasing knowledge about the human genome, it has become feasible to identify the chromosomal location of individual susceptibility genes for complex traits like MDD and even potentially isolate the genes themselves. While these techniques (linkage and association analysis) have proved to be relatively successful for simple Mendelian disorders and for a couple of complex disorders (e.g., Alzheimer's disease), few unequivocal findings have emerged for the major psychiatric disorders. Difficulty in replication may stem for a variety of causes, some inherent to the disorders under study and others resulting from the research methods employed. Complex disorders, of which MDD is a good example, are likely to involve a relatively large number of individual genes, none of which may themselves have a major impact on risk. Furthermore, these genes may interact either with each other and/or with environmental risk factors to produce illness. Certain genetic risk factors may only express themselves at particular developmental phases (e.g., puberty). Of the many conceptual and statistical problems facing this field of complex disease genetics, one of the most critical has been that of multiple testing. With many markers, multiple possible phenotypes and a bewildering array of available statistical methods, applied to small and often under-powered samples, it can be predicted from statistical principles that a high proportion of observed positive results obtained at traditional levels of statistical significance will be false positives.

Traditional approaches to gene detection may not succeed with disorders like MDD. Larger samples and a range of new statistical techniques—some of which will have to address critically the problem of distinguishing false versus true "positive" findings—will need to be applied. No association or linkage findings on MDD have, to date, been sufficiently replicated to be considered established.

Toward an Understanding of the Anatomical and Physiological Basis of Depression

Whereas transient mood changes are experienced by all humans and intense depression can follow a traumatic experience or the loss of a loved one, depression can also be a symptom of many medical conditions, including stroke, Cushing's disease, hypothyroidism, multiple sclerosis, Huntington's disease, and Parkinson's disease. Likewise, depression can also be precipitated by pharmacological agents such as reserpine, which depletes dopamine at synapses. Further support for biological bases of major depressive disorder (MDD) stems from some of the key symptoms of the disorder itself, which include dysregulations of circadian rhythms, cognitive processing, and both appetitive and psychomotor functioning.

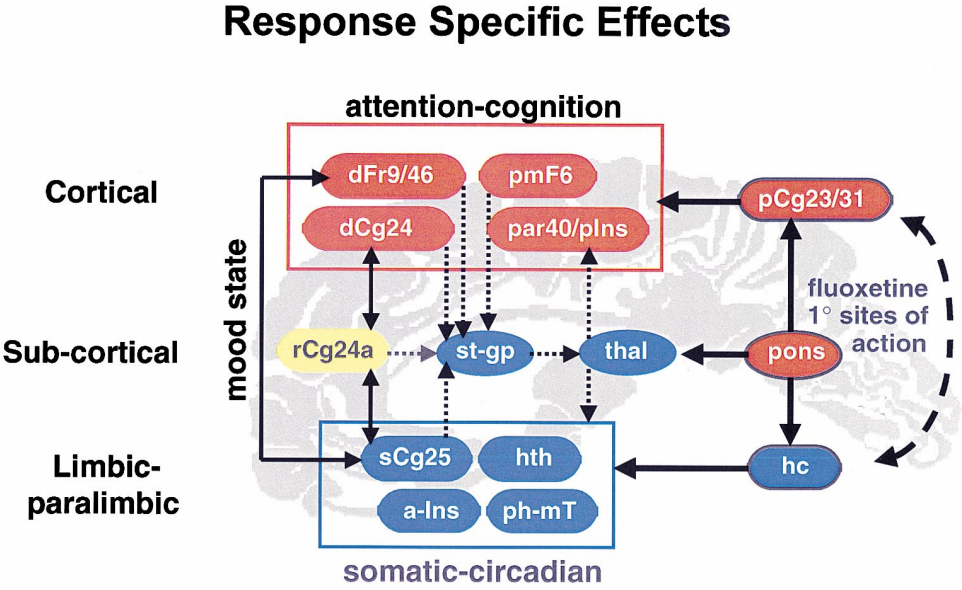

Figure 1. Response-Specific Effects

Schematic model illustrating relationships among regions mediating treatment response. Regions with known anatomical and functional connections that also show significant changes in regional brain glucose metabolism are shown. These were measured using positron emission tomography in hospitalized unipolar depressed patients following 6 weeks of fluoxetine treatment. Blue regions signify areas with a net metabolic decrease with treatment; red areas are those with a net increase. Yellow signifies an area that is hypermetabolic pretreatment and unchanged by treatment. Primary sites of action of fluoxetine are distinguished by a black border. Solid black arrows identify known reciprocal cortico-limbic, limbic-paralimbic, and cingulate-cingulate connections. Dotted small black arrows indicate known cortical-striatal-thalamic pathways. The model proposes that illness remission occurs when there is inhibition of paralimbic and subcortical regions and activation of previously hypofunctioning dorsal areas, an effect facilitated by fluoxetine action in dorsal raphe, hippocampus, and posterior cingulate. Normal or abnormal functioning of rostral cingulate (Cg24) with its bidirectional connections to both anterior cingulate (Cg24) and subgenual cingulate (Cg25) is postulated to facilitate interactions between dorsal cortical and more ventral paralimbic systems and strategically influence pharmacologically mediated changes in serotonergic neurotransmission across the network. The pattern of metabolic change seen in responders is not merely the correction of pretreatment abnormalities. Response to treatment, and remission or recovery, are characterized by normalization of cortical hypometabolism, but persistent subgenual cingulate (Cg25) and hippocampal hypometabolism and rostral cingulate (Cg24a) hypermetabolism (Cg24a), compared to normal subjects. Abbreviations: Red, dFr9/46: dorsolateral prefrontal; par40-pIns: inferior parietal-posterior insula; dCg24: dorsal anterior cingulate; pCg23/31: posterior cingulate. Blue, Cg25: subgenual cingulate; Hth: hypothalamus; aIns: anterior insula; ph-mT: parahippocampus-medial temporal; st-gp: caudate-putamen-globus pallidus; thal: thalamus; Hc: hippocampus. Yellow, rCg24a: rostral anterior cingulate; numbers are Brodmann designations. Figure and caption are closely adapted from Mayberg et al., 2000 and Mayberg et al., 1998, with the authors' permission.

Although the anatomical and physiological basis of depression is still the subject of extensive investigation, major depression (unipolar or bipolar) most likely involves the limbic structures (in circuits involving the cingulate-hippocampus-mamillary bodies-anterior thalamus-cingulate), reward circuits (Nucleus Accumbens, Sublenticular Extended Amygdala, Amygdala, Ventral Tegmentum, Cingulate, Insula, Thalamus, Parahippocampal Gyrus, and Prefrontal cortex), hypothalamus, and anterior temporal cortex (see Figure 1 [Mayberg, 1997]). Patients with strokes that affect right frontal regions may present with moods of indifference/apathy or euphoria, whereas patients with stroke damage in the corresponding left frontal regions may have anxiety or depression.

Although mood states such as depression had been traditionally regarded to be governed solely by the limbic system of the brain, there is now significant evidence for the involvement in depression of numerous nonlimbic central nervous system structures as well. As Soares and Mann (1997) elucidate in their review of the literature, the best replicated structural neuroimaging findings in MDD have included focal white matter hyperintensities in regions associated with the frontal cortex and basal ganglia, and decreased bilateral frontal volumes as well as caudate and putamen volumes. Functional neuroimaging studies with SPECT and PET have evidenced a decrease in global metabolism, with specific decreases in the frontal regions—most consistently the dorsolateral and medial–prefrontal cortex, basal ganglia, and cingulate cortex (Dougherty and Mayberg, 2000). Blood flow and metabolism in MDD patients, however, appears to be increased in portions of orbital frontal cortex and amygdala (Drevets, 1999). In addition to the neuroimaging-based evidence for the role of the basal ganglia–thalamocortical circuitry in the pathophysiology of MDD, more recent functional neuroimaging studies of antidepressant treatment response have suggested that the anterior cingulate cortex may also play a significant role (Buchsbaum et al., 1997).

There is also significant evidence, at least in the more severe forms of MDD, for an enhanced activity of the hypothalamic-pituitary-adrenocortical (HPA) system in MDD. This enhanced activity has been associated with a greater frequency of episodic release of cortisol, marked reductions in bone mineral density compared

to matched controls, and increased adrenal gland volumes. Evidence has also emerged that corticosteroid receptor function is impaired in many patients with major depression and in many healthy individuals at increased genetic risk for an depressive disorder (Holsboer, 1999). Furthermore, clinical and preclinical data suggest that unrestrained secretion of corticoctropin-releasing hormone (CRH) in the CNS produces several signs and symptoms of depression through continuous activation of CRH(1) receptors (Zobel et al., 2000). This has led to the development of drugs that selectively antagonize CRH(1) receptors and to the testing of such compounds in the treatment of MDD (Zobel et al., 2000). Xie and McCobb (1998) provide insights into how adrenocorticotropic hormones produced in the pituitary control the excitable properties of epinephrine-secreting cells of the adrenal gland (by regulating alternative splicing of the Ca^{2+}-activated K^{+} channel, Slo messenger RNA); a similar mechanism may regulate cortisol synthesis and/or secretion. Hypercortisolemia may also be responsible for causing damage to the hippocampus, as suggested by a recent study showing smaller left hippocampal volumes in depression (Bremner et al., 2000). In general, however, the amounts of corticosteroid levels in MDD are probably not as high as the levels observed in stressed primates that suffer hippocampal damage (Sapolsky et al. 1990). Stress also results in the release of substance P from the amygdala, and there is preliminary evidence in humans of antidepressant activity of substance P antagonists.

Monoamines have been the primary focus of the earlier etiological theories of MDD. Although the monoamine depletion hypothesis now seems to be an oversimplified view of the pathophysiology of MDD, one should acknowledge the historical significance of the hypothesis, in that it has helped to develop several new antidepressant drugs, each possessing the capability of affecting the monoamine system in a relatively selective manner. In particular, the putative role of serotonin in MDD has been extensively studied, partly because of the broad therapeutic effects in depression of drugs such as the selective serotonin reuptake inhibitors. Some, but not all, studies have shown reduced endocrine responses to indirect or direct serotonin agonists, and a recent PET study has shown that the blunting in one of these challenges may reflect blunted metabolic changes in the orbital–frontal, adjacent ventral–medial, and cingulate cortex (Siever et al., 1999). Postmortem studies have shown both an increase in the density of serotonin 5-HT-2 receptor binding sites, and a decreased number of serotonin 5-HT transporter binding sites in brain tissue of depressed patients and suicide victims (Owens and Nemeroff, 1994), as well as an increase in the serotonin 5-HT-1A autoreceptors in the midbrain dorsal raphe of suicide victims with major depression (Stockmeier et al., 1998). This postmortem evidence for decreased serotonergic activity in MDD is further supported by the results of recent imaging studies which have evidenced widespread reductions in serotonin 5-HT-1A autoreceptor binding with positron emission tomography (Sargent et al., 2000) and a reduction in the density of brain serotonin transporter binding sites among depressed patients with single photon emission computed tomography (Malison et al., 1998).

Other neurotransmitter systems have also been investigated. Postmortem studies have shown a selective increase in the high-affinity conformation of the brain α-2A-adrenoceptors as well as decreased binding to norepinephrine transporters in the locus coeruleus of depressed patients (Klimek et al., 1997). The latter finding was interpreted as suggesting a compensatory downregulation of this transporter protein in response to an insufficient availability of norepinephrine at the synaptic level (Klimek et al., 1997). The enhanced growth hormone release in response to pyridostigmine challenge in MDD has also been interpreted as suggesting a dysregulation in the acetylcholine neurotransmitter system, providing further support to animal studies linking depression with this system (Tizabi et al., 2000), while the role of dopamine neurotransmission in depression has been studied less extensively. In vivo receptor labeling studies have shown increased dopamine D2 binding in the right striatum of MDD patients, although a recent study has found higher striatal dopamine transporter density in major depression.

Since the beneficial effects of antidepressant drugs or ECT are observed after several weeks, investigators have proposed that these treatments require changes in transcription factors and gene expression (Duman et al., 1997). One hypothesis is that the antidepressant drugs elevate levels of brain-derived neurotrophic factor through cAMP and CREB-mediated effects of transcription of BDNF message (Duman, Heninger, and Nestler, 1997). Ultimately, however, the antidepressants may alter synaptic function and circuit activity as has been postulated to occur in addiction (Berke and Hyman, 2000).

Treatment

Several treatment approaches to MDD are currently available. These approaches include psychotherapy, antidepressant medications, electroconvulsive treatment (ECT), and other somatic therapies. Table 1 summarizes the advantages and disadvantages of these treatments. Although very effective, the use of ECT is mostly limited to patients with MDD who are either highly resistant to treatment, or psychotic, and the efficacy of other somatic therapies has not been established yet. In the realm of psychotherapy, two types of time-limited psychotherapy have been shown consistently to be effective in treating MDD, interpersonal psychotherapy and cognitive therapy. Pharmacotherapy has shown to be an effective treatment for MDD, with 21 drugs having been approved by the Food and Drug Administration for the treatment of depression based on double-blind, placebo-controlled studies. The study of the efficacy of these agents already marketed for depression and of newer agents under investigation has been complicated by the relatively high response rates to placebo in controlled trials, the inadequate duration of treatment in some studies (Quitkin et al., 1986), and the frequent use of measures of outcome with relatively lesser sensitivity to detect differences between active and inactive treatments (Faries et al., 2000). More recently, a number of compounds with putative antidepressant activity and pharmacological effects distinct from those of the traditional antidepressants, such as substance P antagonism

Table 1. Treatments for Major Depressive Disorder

Treatments	Advantages	Disadvantages
Psychotherapeutic interventions (i.e., cognitive-behavioral therapy, interpersonal psychotherapy, behavioral therapy)	Provides useful conceptual framework, diminishes stigma, high patient acceptance.	Providers of these specific forms of psychotherapy, which have proven efficacy in MDD, are somewhat limited; more commonly practiced forms of psychotherapy (i.e., psychodynamic, supportive) typically show marginal efficacy and little empirical data demonstrating improved symptoms.
Traditional pharmacological approaches:		
Selective serotonin reuptake inhibitors (SSRIs): *citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline*	Proven antidepressant efficacy; their primary pharmacological action is the blockade of uptake of serotonin (5-HT), with varying degree of specificity; first-line treatment for the great majority of practitioners; good patient acceptance mostly due to favorable side-effect profile.	Although the short-term tolerability is very good, long-term treatment can be associated with bothersome side-effects such as sexual dysfunction, weight gain, insomnia, somnolence, and apathy.
Atypical antidepressants: *bupropion, mirtazapine, nefazodone, and trazodone*	Proven antidepressant efficacy; their pharmacological actions vary greatly, with bupropion affecting primarily norepinephrine (NE) and dopamine (DA) neurotransmission, mirtazapine affecting 5-HT and NE neurotransmission, and nefazodone and trazodone being serotonin 5-HT2 receptor antagonists associated with mild reuptake inhibition of 5-HT and NE.	Although sexual dysfunction and, in the case of nefazodone and bupropion, weight gain seem less common during long-term treatment with these agents than with SSRIs, the risk for sedation in the case of trazodone and mirtazapine, and the need for b.i.d. dosing in the case of nefazodone and bupropion may have somewhat limited the use of these agents as first line treatment.
Serotonin norepinephrine reuptake inhibitors (SNRIs): *Venlafaxine*	Proven antidepressant efficacy; primary pharmacological action is the blockade of 5-HT uptake at lower doses, and a blockade of both 5-HT and NE uptake at higher doses.	As with the SSRIs, although the short-term tolerability is good, long-term treatment can be associated with bothersome side-effects such as sexual dysfunction, weight gain, insomnia, and somnolence.
Selective norepinephrine reuptake inhibitors (SNRIs): *Reboxetine*	Proven antidepressant efficacy; primary pharmacological action is the blockade of NE uptake.	Not yet approved by the FDA and therefore available in the U.S.; mild anticholinergic side-effects and tachycardia.
Tricyclic and tetracyclic antidepressants: *amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline and trimipramine*	Proven antidepressant efficacy; they used to be the gold standard of pharmacological treatment	No longer first-line treatment; limited patient acceptance mostly due to high rates of anticholinergic side effects, sedation, orthostatic hypotension, and weight gain; they also affect cardiac conduction and are lethal in overdose.
Monoamine oxidase inhibitors: *isocarboxazid, phenelzine, and tranylcypromine*	Proven antidepressant efficacy; particularly efficacious in the atypical form of MDD (i.e., mood reactivity accompanied by hyperphagia, hypersomnia, extreme fatigue, and/or hypersensitivity to rejection.	Very limited patient acceptance mostly due to requirement of tyramine-free diet (to minimize the risk of hypertensive crises) and the possibility of severe, life-threatening drug–drug interactions; they are also lethal in overdose.
Newer pharmacological agents:		
Neutraceuticals: *hypericum, SAMe*	Promising open data and double-blind studies with relatively small number of subjects.	No proven efficacy yet; treatment not covered by insurance.
Substance P antagonists	Promising double-blind studies.	Under development.
CRF antagonists	Promising open data in a small number of subjects.	Under development.
Serotonin 5-HT1A partial agonists: *Gepirone*	Promising double-blind studies.	Currently in phase III of development.
Electroconvulsive therapy	Extremely effective even in treatment-resistant cases and in depression with psychotic features.	Very low patient acceptability; significant effects on memory and cognitive function; procedures can be aversive to patients.
Other somatic therapies:		
Neurosurgical procedures: *(e.g., cingulotomy)*	Promising data from a small number of subjects with refractory depression.	Invasive medical procedure with the potential for high-risk side effects. Best procedures remain to be established.
Transcranial magnetic stimulation (TMS)	Noninvasive procedure; promising data from a small number of subjects with refractory depression.	Limited open data in a small number of subjects; best stimulation parameters for TMS remain to be established.
Vagus nerve stimulation (VNS)	Promising treatment for refractory depression based on open study data; no evidence of cognitive impairment.	Invasive procedure requiring surgery; hoarseness during device activation; battery needs replacement every 7–10 years.

See Fava and Rosenbaum (1995) and Jarrett and Rush (1994) for details.

and corticosteroid releasing factor (CRF) antagonism, are currently being developed and may further expand our current pharmacopoea. The rationale for evaluating the antidepressant potential of these new agents comes from both preclinical and clinical studies, such as in the case of the well-documented HPA axis hyperactivation, which has led to the development of CRF antagonists or the effect of tricycic antidepressants on Substance P.

Antidepressant drugs are typically classified on the bases of their effects on the neuronal synapses, such as the blockade of the reuptake of neurotransmitters or the inhibition of the monoamine oxidase enzymes (Fava and Rosenbaum, 1995). The only exception is the tricyclic antidepressant (TCA) group, which is identified on the basis of its distinctive chemical structure, and is known to have relatively higher norepinephrine reuptake inhibiting activity, relatively lower 5-HT reuptake inhibiting effect (with the exception of clomipramine), and to block several neurotransmitter receptors. These types of classifications of antidepressant drugs have focused too narrowly on synaptic pharmacology, and have failed to address the molecular and cellular changes in neural functioning that are brought on as adaptations to chronic administration of antidepressant drugs (Hyman and Nestler, 1996). Such changes in postreceptor signal transduction may account for the characteristic delay in onset of efficacy with antidepressant treatment, with a lag phase typically of at least 2 weeks. Alternatively, one could postulate that this lag phase may be related to a reorganization of networks of neurons.

Despite the availability of effective treatment, we are still faced with the dilemma that MDD is widely underrecognized and undertreated in the community (1990). Approximately 50% of all MDD outpatients initially exposed to either a time-limited psychotherapy targeted for depression, or to a single antidepressant medication, respond to treatment. The remaining 50% continue to experience symptoms and remain functionally impaired after the initial treatment level (Fava and Davidson, 1996). This large percentage of initial nonresponders presents a significant challenge to clinicians, who must seek out additional therapeutic measures in at least 50% of their patients in order to achieve response (Thase and Rush, 1995). This next-step treatment, employed after the patient does not initially respond, has not been studied in any systematic fashion (although there are controlled clinical trials of certain treatment strategies such as lithium augmentation of antidepressants) and is the focus of an ongoing NIMH multicenter study (Sequenced Treatment Alternatives to Relieve Depression) that involves the enrollment and 12 month follow-up of over 4000 patients.

Conclusion

In summary, MDD is a highly prevalent major medical whose pathophysiology is still poorly understood. MDD is often recurrent or chronic, and evidence suggests that genetic factors partially influence overall risk of illness but also influence the sensitivity of individuals to the depressogenic effects of environmental adversity. Treatment with antidepressants, ECT, or certain forms of psychotherapy is fairly effective, but a substantial proportion of patients do not respond adequately, thereby requiring subsequent interventions. There are still many unanswered questions about MDD: (1) What are the susceptibility genes and their environmental modifiers? (2) What are the pathophysiologies of the neural systems underlying this complex disorder? (3) How do we understand the therapeutic mechanisms underlying the currently available pharmacological and ECT approaches? And (4) how do we improve our success rate in treating this highly disabling medical condition and how can we develop more rational algorithms for those who do not respond to standard treatments? Future investigations need to keep these issues in mind.

References

Berke, J.D., and Hyman, S.E. (2000). Addiction, dopamine, and the molecular mechanisms of memory. Neuron *25*, 515–532.

Blazer, D.G., Kessler, R.C., McGonagle, K.A., and Swartz, M.S. (1994). The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. Am. J. Psychiatry *151*, 979–986.

Bremner, J.D., Narayan, M., Anderson, E.R., Staib, L.H., Miller, H.L., and Charney, D.S. (2000). Hippocampal volume reduction in major depression. Am. J. Psychiatry *157*, 115–118.

Buchsbaum, M.S., Wu, J., Siegel, B.V., Hackett, E., Trenary, M., Abel, L., and Reynolds, C. (1997). Effect of sertraline on regional metabolic rate in patients with affective disorder. Biol. Psychiatry *41*, 15–22.

Dougherty, D.D., and Mayberg, H.S. (2000). Neuroimaging studies of treatment response in major depression. In Contemporary Strategies in Psychiatric Neuroimaging Research, D.D. Dougherty and S.L. Rauch, eds. (Washington D.C.: American Pyschiatric Press), in press.

Drevets, W.C. (1999). Prefrontal cortical-amygdalar metabolism in major depression. Ann. NY Acad. Sci. *877*, 614–637.

Duman, R.S., Heninger, G.R., and Nestler, E.J. (1997). A molecular and cellular theory of depression. Arch. Gen. Psychiatry *54*, 597–606.

Faries, D., Herrera, J., Rayamajhi, J., DeBrota, D., Demitrack, M., and Potter, W.Z. (2000). The responsiveness of the Hamilton Depression Rating Scale. J. Psychiatr. Res. *34*, 3–10.

Fava, M., and Rosenbaum, J.F. (1995). Pharmacotherapy and somatic therapies. In Handbook of Depression, E.E. Beckham and W.R. Leber, eds. (New York: Guilford Publications), pp. 280–301.

Fava, M., and Davidson, K.G. (1996). Definition and epidemiology of treatment-resistant depression. In The Psychiatric Clinics of North America: Treatment Resistant Depression, Vol. 19, 179–200.

Holsboer, F. (1999). The rationale for corticotropin-releasing hormone receptor (CRH-R) antagonists to treat depression and anxiety. J. Psychiatr. Res. *33*, 181–214.

Hyman, S.E., and Nestler, E.J. (1996). Initiation and adaptation: a paradigm for understanding psychotropic drug action. Am. J. Psychiatry *153*, 151–162.

Jarrett, R.B., and Rush, R.J. (1994). Short-term psychotherapy of depressive disorders: current status and future directions. Psychiatry. Interpers. Biol. Proc. *57*, 115–132.

Kendler, K.S., Kessler, R.C., Walters, E.E., MacLean, C.J., Sham, P.C., Neale, M.C., Heath, A.C., and Eaves, L.J. (1995). Stressful life events, genetic liability and onset of an episode of major depression in women. Am. J. Psychiatry *152*, 833–842.

Kendler, K.S., Gardner, C.O., and Prescott, C.A. (1999). Clinical characteristics of major depression that predict risk of depression in relatives. Arch. Gen. Psychiatry *56*, 322–327.

Kessler, R.C. (1997). The effects of stressful life events on depression. Annu. Rev. Psychol. *48*, 191–214.

Klimek, V., Stockmeier, C., Overholser, J., Meltzer, H.Y., Kalka, S., Dilley, G., and Ordway, G.A. (1997). Reduced levels of norepinephrine transporters in the locus coeruleus in major depression. J. Neurosci. *17*, 8451–8458.

Malison, R.T., Price, L.H., Berman, R., Van Dyck, C.H., Pelton, G.H., Carpenter, L., Sanacora, G., Owens, M.J., Nemeroff, C.B., Rajeevan, N., et al. (1998). Reduced brain serotonin transporter availability in major depression as measured by [123I]-2 beta-carbomethoxy-3beta-(4-iodophenyl-tropane and single photon emission computed tomography. Biol. Psychiatry *44*, 1090–1098.

Mayberg, H.S. (1997). Limbic-cortical dysregulation: a proposed model of depression. J. Neuropsychiatry Clin. Neurosci. *9*, 471–481.

Mayberg, H.S., Liotti, M., Brannan, S.K., McGinnis, S., Jerabek, P., Martin, C.C., and Fox, P.T. (1998). Disease and state-specific effects of mood challenge on rCBF. NeuroImage *7*, S901.

Mayberg, H.S., Brannan, S.K., Tekell, J.L., Silva, J.A., Mahurin, R.K., McGinnis, S., and Jerabek, P.A. (2000). Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. Biol. Psychiatry *48*, 830–844.

Mueller, T.I., and Leon, A.C. (1996). Recovery, chronicity, and levels of psychopathology in major depression. Psychiatr. Clin. North Am. *19*, 85–102.

Murray, C.J., and Lopez, A.D. (1996). Evidence-based health policy—lessons from the Global Burden of Disease Study. Science *274*, 740–743.

Owens, M.J., and Nemeroff, C.B. (1994). Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. Clin. Chem. *40*, 288–295.

Quitkin, F.M., Rabkin, J.G., Stewart, J.W., McGrath, P.J., and Harrison, W. (1986). Study duration in antidepressant research: advantages of a 12-week trial. J. Psychiatr. Res. *20*, 211–216.

Sapolsky, R.M., Uno, H., Rebert, C.S., and Finch, C.E. (1990). Hippocampal damage associated with prolonged glucocorticoid exposure in primates. J. Neurosci. *10*, 2897–2902.

Sargent, P.A., Kjaer, K.H., Bench, C.J., Rabiner, E.A., Messa, C., Meyer, J., Gunn, R.N., Grasby, P.M., and Cowen, P.J. (2000). Brain serotonin1A receptor binding measured by positron emission tomography with [11C]WAY-100635: effects of depression and antidepressant treatment. Arch. Gen. Psychiatry *57*, 174–180.

Siever, L.J., Buchsbaum, M.S., New, A.S., Spiegel-Cohen, J., Wei, T., Hazlett, E.A., Sevin, E., Nunn, M., and Mitropoulou, V. (1999). D,L-Fenfluramine response in impulsive personality disorder assessed with [18F]fluorodeoxyglucose positron emission tomography. Neuropsychopharmacology *20*, 413–423.

Soares, J.C., and Mann, J.J. (1997). The anatomy of mood disorders—review of structural neuroimaging studies. Biol. Psychiatry *41*, 86–106.

Stockmeier, C.A., Shapiro, L.A., Dilley, G.E., Kolli, T.N., Friedman, L., and Rajkowska, G. (1998). Increase in serotonin-1A autoreceptors in the midbrain of suicide victims with major depression—postmortem evidence for decreased serotonin activity. J. Neurosci. *18*, 7394–7401.

Sullivan, P.F., Neale, M.C., and Kendler, K.S. (2000). The genetic epidemiology of major depression: review and meta-analysis. Am. J. Psychiatry *157*, 1552–1562.

Thase, M.E., and Rush, A.J. (1995). Treatment resistant depression. In Psychopharmacology: Fourth Generation of Progress, F.E. Bloom and D.J. Kupfer, eds. (New York: Raven Press), pp. 1081–1097.

Tizabi, Y., Rezvanil, A.H., Russell, L.T., Tyler, K.Y., and Overstreet, D.H. (2000). Depressive characteristics of FSL rats: involvement of central nicotinic receptors. Pharmacol. Biochem. Behav. *66*, 73–77.

Tsuang, M.T., and Faraone, S.V. (1990). The Genetics of Mood Disorders (Baltimore, MD: The Johns Hopkins University Press, 1990).

Xie, J., and McCobb, D.P. (1998). Control of alternative splicing of potassium channels by stress hormones. Science *280*, 443–446.

Zobel, A.W., Nickel, T., Kunzel, H.E., Ackl, N., Sonntag, A., Ising, M., and Holsboer, F. (2000). Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. J. Psychiatr. Res. *34*, 171–181.