DEPRESSION

Treatment Strategies and Management

SECOND EDITION

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Depression

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Second Edition

Edited by

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Foreword

Drs. Schwartz and Peterson have done it again. In the second edition of their book on depression, they have updated their first volume and put together a comprehensive and up-to-date analysis of the state of the art for major depressive disorder. This is an excellent compendium for clinicians, starting with a description of the syndrome and its etiology and epidemiology and expanding with additional chapters venturing into the genetics and modern neuroimaging of depression.

Perhaps the most useful new direction of this updated volume is how it now covers a whole host of topics that overlap with depression but are rarely found together in one place: psychotic depression; geriatric depression; and depression with anxiety, pain, personality disorders; medical comorbidities; and substance abuse, all in dedicated chapters. Useful and often neglected topics such as compliance as well as using outcome measurements in clinical practice are additional and unique additions to the book.

As before, treatment is an important emphasis of this book. Therapeutic approaches have been extensively broadened and updated. Not only are the expected antidepressant drugs covered, but also the evidence for the strengths and limitations of antidepressant treatments emerging from the STAR*D study is presented. Natural products are also covered. Perhaps one of the best reviews of the evidence base for treating resistant depression is put together in a particularly impressive chapter. Long-term outcomes not only from antidepressants but also from psychotherapy are discussed in another key contribution. Finally, authors discuss the emergence of neuromodulation therapies, beyond electroconvulsive therapy, now to the rise and fall of vagal nerve stimulation and currently the dawning of clinical applications of the newly approved transcranial magnetic stimulation are presented. Glimpses of the potential for deep brain stimulation are given as well.

In sum, the reader will enjoy a useful and comprehensive approach to depression and its treatment and will again emerge well informed from a scholarly yet practical approach.

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1 Depression: Phenomenology, Epidemiology, and Pathophysiology

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INTRODUCTION

The core elements of what we now call major depressive disorder (MDD) are as old as the history of humankind. Hippocrates (460–377 BC) described melancholia, a condition that was very similar to today's MDD specifier of the same name (1): prolonged despondency, blue moods, detachment, anhedonia, irritability, restlessness, insomnia, aversion to food, diurnal variation, and suicidal impulses. Mourning and grief were viewed as normal responses to loss, and only the presence of excessive, psychotic, or unmotivated sadness was construed as "disordered." This distinction was maintained for many years in the definition of "depressive neurosis" as described in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-II (2). Starting with DSM-III (3), however, theoretical underpinnings of the causes of mental illnesses, including MDD, were removed. Mental illnesses were now conceptualized as symptom-based, categorical diseases (4).

This nonetiological and atheoretical classification greatly improved the reliability of depressive disorder diagnosis by reducing diagnostic variability between clinicians. The only exception included in DSM-IV (1, p. 740) refers to the two-month interval after the death of a loved one, during which a depressive state is diagnosed as bereavement.

Despite this improvement, MDD is a heterogeneous condition with fluctuating symptoms over time. There is a continuing need to more reliably subdivide MDD into clinically meaningful subtypes that are more predictive of treatment response.

PHENOMENOLOGY OF DEPRESSIVE STATES

The psychic functional problems encountered by depressed individuals are extensive and not limited to the affective domain. We will see that there is a wealth of possible descriptors of individual depressive states that are not necessarily diagnostic (5).

MDD's central descriptive features refer to the disturbance of feelings and affective states. Exhibiting a "depressed mood" may vary greatly in terms of individual experience. There may be alterations in the way one's body experiences a "bodily feeling" or a "vital feeling." Sadness may be described at a very vague physical level such as the feeling of "pressure" or "misery." A common presentation is with "feelings of insufficiency," a sense of diminished capacity or "self-esteem." In addition, there is often a lowering of the "executive" abilities to understand, think, make decisions, and act with the emergence of the feeling of being incompetent, useless, or worthless.

In other cases there may be an increased indifference to the environment with a decreased reactivity to stimuli, and the inability to experience pleasurable events, called anhedonia. Severe cases of anhedonia may be accompanied by apathy, or an absence of any feeling. Apathy, in turn, may lead to a lack of will to act. In these cases the patient may passively endanger himself or herself by not eating, not avoiding other possible noxious situations, or not looking out for his or her best interests. In context of lack of joy (anhedonia), loss of feelings (apathy), and lack of will to act (abulia), the future is often construed as hopeless. This may be a particularly vulnerable period for the emergence of recurrent thoughts about death and possible suicide.

Often there are changes in other psychic phenomena such as perception, experience of space and time, thinking, and self-awareness. Alterations of the emotional tone of perception are relatively common experiences for the depressed individual. Habitual objects, the environment as a whole, or sometimes even the "self" may appear different, often with an unsatisfactorily, frustrating quality. Things may not look the same as before, and a sense of derealization may emerge. Time may seem to have stopped, and generally time awareness may lose reliability. Hallucinations and delusions are possible. In severe cases, reality testing will be affected and various cognitive distortions may be present, affecting the patient's mental capacity. Spanning a large interval from transient thoughts of worthlessness and hopelessness to entrenched delusions of sin and guilt, emerging psychosis and thought disturbance may be comparable to that seen in schizophrenic spectrum disorders. The above symptomatology illustrates the potential heterogeneity of depressive disorders.

CLASSIFICATION OF THE DEPRESSIVE STATES

Given the phenomenology noted above, individual clinical presentations may vary, so do the course, prognoses, and treatment. Now that we better understand the breadth of the phenomenology of MDD, the ability to move toward a categorical and defining set of depressive symptoms is warranted.

The following table includes the categorical variants of depressive states included in DSM-IV-TR™ (1, pp. 349–376).

DSM-IV-TR depressive states	
Major depressive episode (not a diagnostic per se)	
Major depressive disorder (single episode or recurrent)	296.2× or 296.3×
Dysthymic disorder	300.4
Bipolar I disorder (most recent episode depressed or mixed)	296.5×, 296.6×
Bipolar II disorder (most recent episode depressed or mixed)	296.89
Cyclothymic disorder	301.13
Mood disorder due to general medical condition (with depressive features or with major depressive-like episode)	293.83
Substance-induced mood disorder (with depressive or mixed features)	
Bipolar disorder NOS	296.80
Depressive disorder NOS	311.0
Adjustment disorder (with depressed mood, mixed anxiety and depressed mood, or mixed disturbance of emotions and conduct)	309.0, 309.28, or 309.4
Comorbid conditions	

DSM-IV-TR Appendix B—new categories proposals for depressive states
Postpsychotic depressive disorder of schizophrenia
Minor depressive disorder
Recurrent brief depressive disorder
Mixed anxiety-depressive disorder
Depressive personality disorder

Differential Diagnosis of the Depressive States

In the DSM-IV-TR (1, pp. 349–376), the central diagnostic building block is the major depressive episode (MDE). An MDE is present when the patient exhibits five of the nine symptoms as a discrete presentation lasting at least two weeks. The symptoms are depressed mood, diminished interest or pleasure in activities, loss of appetite or weight loss, sleep disturbance as insomnia or hypersomnia, psychomotor agitation or retardation, loss of energy, feelings of worthlessness or guilt, poor concentration, and recurrent thoughts about death or suicidal ideation, plan, or intent. Depressed mood or diminished interest (or pleasure in activities) must be one of the first criteria. Defining the threshold for disorder would suggest that symptom severity be high enough to affect the patient's psychosocial functioning.

If a patient is experiencing a first MDE in his or her lifetime, MDD single episode is diagnosed. Conversely, if previous episodes have been present, MDD recurrent is considered. Additional specifiers will indicate the intensity of the condition (mild, moderate, severe, or with or without psychotic features), the presence of particular clinical variants (catatonic, melancholic, atypical, or in postpartum), or the longitudinal variability (partial or full remission or the presence of seasonal patterns) may be used for a more accurate diagnosis.

If MDE is experienced in the context of history of at least one manic episode, mixed episode, or hypomanic episode, then a diagnosis of bipolar I disorder or bipolar II disorder may be made.

Dysthymic disorder is defined as having a depressed mood present, more days than not, for two years (one year in children and adolescents) in the presence of other associated symptoms of depression. The patient has to have at least two of the following six symptoms: appetite disturbance, sleep disturbance, low energy, low self-esteem, poor concentration, and feelings of hopelessness. Functioning in dysthymic disorder is less impacted than in MDE.

Special attention in diagnosing needs to be paid to the presence of pertinent, clearly identifiable causes of distress such as medical conditions, substance abuse or dependence, bereavement, or other stressors as in adjustment disorders. In these areas treatment options and prognosis may differ widely. Residual categories are represented by depressive disorder and bipolar disorder not otherwise specified (NOS). Use of "NOS" designation is indicated when ultimate diagnosis is unclear, as the criteria for the period or the number of distinct symptoms are not fulfilled.

It is important to note that it may be difficult to cluster the symptoms under the single diagnosis of MDD because the comorbidity of depression with medical illness, substance abuse, and anxiety seems to be high. For example, the comorbidity of anxiety is over 30% (6). Of course, such complicated clinical presentations also affect prognosis and treatment course as well.

Interest has also developed in some prognostically difficult areas, and research has been dedicated to the relationship between depression and somatization (7), trauma (8), dissociation (9), and borderline personality disorder (10). It may often be very difficult to tease out the medical symptomatology of the former from the enduring symptoms of chronic, empty depression, and self-injurious thoughts and behaviors of the latter.

Epidemiological Information

The lifetime prevalence of the MDD is 10% to 25% for women and between 5% and 12% in men (11,12). After the first episode of depression the female to male risk tends to become equal for recurrent depression. These overall figures are significantly higher than the prevalence for bipolar disorders, which is roughly 0.4% to 1.6%. Bipolar illness is thought to be a more severe and pervasive illness, but MDD is also now felt to be chronic and ultimately affecting more individuals. Most MDD patients will have an onset between the ages of 20 and 40 years. Depression, today, is the second leading cause of burden of the disease in the 15 to 44 years age category (13).

Some risk and predictive factors for MDD have been cited. Being admitted to a hospital or a long-term care facility, as well as having an increased number of outpatient visits for somatic reasons, tends to increase the risk for depression or at least its detection (14,15). Other risk factors may be represented by lower socioeconomic status, separated and divorced status, and presence of excessive social stressors (16). Lastly, correlations with an increased risk for MDD have been made with positive family history (17), the presence of early adverse experiences, and with certain borderline personality attributes (18).

The diagnosis of depression in the elderly poses significant public health problems, as this clinical population is expanding at a phenomenal rate. Risk factors in the geriatric population include female sex, low socioeconomical level, bereavement, prior depression, medical comorbidities and disability, cognitive deterioration, and vascular factors (19).

Finally, the greatest risk associated with MDD is the threat of suicide, both attempted and completed. Thirty percent of completed suicide cases have a mood disorder diagnosis (20,21). Moreover, MDD is associated with much social disability, and the lifetime risk of death by suicide may be as high as 15% (22). As mentioned earlier, the heterogeneous mixture of symptoms that MDD patients experience points to a multifactorial etiology for this disorder, which makes research in this area often difficult. In the modern era, advanced techniques including neuroimaging, molecular genetics, and translational and clinical studies may help to elucidate etiological factors, and thereby determine the ultimate causes of an individual's cluster of MDD symptoms. Improved treatment modalities should follow.

THEORIES OF PATHOPHYSIOLOGY

Theories regarding the etiology of depressive states have been linked inextricably to models of treatment throughout medical history. The rationale for a healer's choice of treatment derives from the need to correct what has gone awry in the sufferer. In prescientific civilizations, mental illnesses were deemed to have resulted from some spiritual or magical force, thus requiring treatment through prayer, sacrifice, or other means (23). With the emergence of science,

theories changed from these concepts to those focused on the body and material causes. The methods of science have advanced tremendously also, resulting in more numerous and effective treatments for depression and other mental illness. However, the etiology of major depression continues to be elusive.

The first recorded theories for a biological basis of major depression were developed in ancient Greece by way of the four humors, as outlined in the *Corpus Hippocraticum*, in the fifth century BC (24). The humors corresponded to components of temperament, so that *yellow bile* was linked to a choleric or irritable temperament, *blood* to being sanguine or cheerful, *phlegm* to a phlegmatic style or stoicism, and *black bile* to melancholy or sadness. When applied to subjects experiencing depression, the theory identified "melancholia," or excessive black bile in the blood, as the root of the problem. Using the logic for which they are justly famous, Greek physicians applied the treatment of phlebotomy to lower the excessive levels of black bile. In a very real sense, these physicians were remedying what they perceived to be a "chemical imbalance." From the perspective of today, we wonder how such treatment could have persisted for over a millennium, given the lowered level of energy and vigor that must have resulted from such declines in hematocrit. Certainly treatment was dramatic, and may have induced additional effects in emotion-processing neurocircuits than the usual nontreatments. The fatigue resulting from the treatment may have led to socially sanctioned relief from work or other stressors. But perhaps there were other biological effects: an alteration in the stress response or immune-modulation systems, release of endogenous opiods or other neurotransmitters, or possibly altered signaling from the vagus nerve to the brain as a result of changes in cardiac functioning stemming from bloodletting. Although we no longer believe there is a black substance in the blood that directly lowers mood, the practice of bloodletting exemplifies how a theory of etiology can lead to an intervention that may lead to improvement in illness, though perhaps for reasons completely unrelated to the theoretical and psychological model of the illness.

The syndrome of melancholia continued to be described throughout the Dark and Middle Ages with little revision. However, St. Augustine's philosophical distinction between the origin of emotional functions and imagination in the "inferior soul," compared with the origin of higher mental functions such as intellect and will in the "superior soul," contributed to a greater level of moral theorizing about depression and mental illness in general (24,25).

Griesinger (1817–1868) argued that mental illness without exception stemmed from somatic changes and attempted to identify relationships between psychological symptoms and brain pathology (25). Later, Emil Kraepelin (1856–1926) laid the foundation for the current classification scheme for psychiatric disorders. He grouped mental illnesses that preserved the premorbid personality of the individual under the category of *manic-depressive illness*, including what we today label bipolar disorder, major depression, and milder forms of mood disturbance (25). *Dementia praecox* (later renamed *schizophrenia* by Eugene Bleuler) was separated from the mood disorders because of its poor long-term prognosis, leading to personality decline.

Sigmund Freud also came to focus his life's efforts on understanding the psychological processes at work in people. His seminal paper, *Mourning and Melancholia*, identified hostility against a psychologically internalized lost object as the root cause of depressive symptoms (26). The rise of psychodynamically

focused psychiatry, in the period around World War II, led to a substantial pause in biological exploration of major depression and other mental illnesses, which regained momentum after the serendipitous discovery of the mood-elevating effects of medications like imipramine. Key names and works that usually surface with regard to the psychological etiology of MDD include Freud, Skinner, Beck, and Sullivan.

Observations of the natural course of various diseases have provided some clues to the biological cause of depression. For example, depressive symptoms emerging from the hypercortisolemia of Cushing's disease, the loss of dopaminergic function in Parkinson's disease, and the thyroid dysfunction in hypothyroidism all suggest a role for these elements in the pathophysiology of major depression. Although the approach of inferring pathophysiology from effective treatments is helpful, treatments may also induce improvement via mechanisms unrelated to the actual cause of the disease, such as diuretics in the treatment of essential hypertension. If a treatment reduces symptomatology without correcting the core pathological process, it is possible the disease may continue to progress until it reaches a point where such treatments are no longer effective. It is helpful to recognize that the foci of biological research into depression pathophysiology have arisen largely from the discovery of effective pharmacological treatments, more so than treatments have emerged from scientific investigation.

A few challenges in exploring the origins of depression include the placebo responsiveness, the remitting nature of the illness, the clinical syndrome of major depression likely representing the final common phenotypic expression of several separate disease processes (endophenotypes), and the limitations in adequately defining clinical subtypes of MDD.

The Biogenic Amine Hypotheses

The biogenic amines consist of naturally occurring biologically active compounds derived from the enzymatic decarboxylation of amino acids. Monoamines are a subset of the biogenic amines consisting of a single NH_2 (amine) group bound to a carbon-containing side chain. The monoamines important in psychiatry are further subdivided into the catecholamines (epinephrine, norepinephrine, and dopamine), the indoleamines (serotonin and tryptophan), and the imidazoleamine (histamine). Neurons that produce these neurotransmitters are localized to specific nuclei in the brain stem: the locus ceruleus for norepinephrine, the raphe nuclei for serotonin, and the ventral tegmental area (VTA) and substantia nigra for dopamine. The tuberomamillary nucleus of the hypothalamus is the site of histaminergic neurons in the brain. In 1954, Bloch and colleagues reported the mood-elevating effects of the monoamine oxidase inhibitor (MAOI) iproniazid, which was used to treat tuberculosis (27). MAO is an enzyme located primarily on the outer mitochondrial membrane, which acts to catabolize the monoamines by removing the amine group. By inhibiting the action of that enzyme, iproniazid slows the breakdown of the monoamine neurotransmitters, leading to synaptic increases in serotonin, norepinephrine, and dopamine. Subsequently, in 1958, three reports emerged of the antidepressant activity of imipramine, which had been developed as an antihistamine, but was being evaluated in schizophrenia on the basis of the benefits displayed by chlorpromazine in this illness (28–30). Imipramine was the first of the class of medications called tricyclic antidepressants (TCAs), acting primarily by

inhibiting reuptake of norepinephrine from the synapse. Joseph Schildkraut proposed in 1965 that the monoamines are likely the key elements in the etiology of depression (31), and loss of these monoamines or imbalance creates MDD. Additional support to this hypothesis derived from the findings that the antihypertensive drug reserpine (which was used to treat hypertension by depleting stores of these amines) could lower mood significantly in people and also induce sedation and motor retardation in animal models of depression. Amphetamine, which releases monoamines into the synapse, was also known to elevate mood. Additional work found norepinephrine to play important roles in concentration, attention, memory, sleep, and appetite, which can all be disrupted in MDD. Stated simply, the *catecholamine hypothesis* proposed that depression may be related to a deficiency in catecholamines, in particular norepinephrine (31). Both elevations and reductions in norepinephrine and its primary CNS metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG), have been demonstrated in the cerebrospinal fluid (CSF), plasma, and urine of depressed patients (32). However, this finding is confounded by the fact that the origin of these metabolites is unknown. Studies of the locus ceruleus have suggested that there is dysregulation at this level of the system also, with the somewhat paradoxical findings of both decreased density of neurons and increased tyrosine hydroxylase activity (33,34). (Tyrosine hydroxylase is the enzyme active in the rate-limiting step in the process of converting the amino acid tyrosine into norepinephrine.) A consistent finding has been the clear downregulation of β-adrenoreceptors in the rat forebrain following longer-term antidepressant treatment with a TCA or electroconvulsive therapy (ECT) (35). The time required for this downregulation to occur in rats is similar to the delayed response to antidepressants in humans, leading to the hypothesis that downregulation of β-receptors is required for antidepressant efficacy.

Closely related to Schildkraut's hypothesis is the *supersensitivity hypothesis*, positing that presynaptic α-2 receptors, which act to inhibit the release of norepinephrine, may be supersensitive in depressed subjects, resulting in reduced overall release of norepinephrine from the locus ceruleus (36). Consistent with this hypothesis have been the reports of increased levels of α-2 receptors in postmortem tissue of depressed patients (37). The sensitivity of α-2 receptors has been explored by using clonidine, a centrally acting α-2 agonist. Activation of postsynaptic α-2 receptors stimulates the release of growth hormone (GH)-releasing hormone (GHRH) from the hypothalamus, subsequently causing GH secretion from the pituitary. Patients with depression have been repeatedly found to have blunted GH release after receiving clonidine, suggesting a disruption in noradrenergic signaling (38,39). One model that attempts to integrate the various findings posits that under resting conditions norepinephrine concentrations may be lower than normal, but with stress there is an exaggerated norepinephrine signal, possibly secondary to supersensitive or upregulated receptors (40). As with the catecholamine hypothesis, this idea emerged from observations that depressed mood could occur following administration of cholinergic agonists or physostigmine (an inhibitor of cholinesterase, an enzyme that metabolizes acetylcholine). However, unlike the demonstrated effect of iproniazid and imipramine to elevate mood in support of the catecholamine hypothesis, administration of anticholinergic medications that lacked effect on monoamine systems did not alleviate depression (41). Although acetylcholine is no longer thought to play a central role in the etiology of depression, the

consistently demonstrated supersensitivity of depressed subjects to cholinergic stimulation suggests that functioning of this system is disturbed in MDD (42).

In 1967, Coppen proposed that another monoamine, serotonin (5-hydroxytryptophan, 5HT), played an important role in major depression as well (43). Coppen demonstrated that the addition of tryptophan (the immediate precursor in the synthesis of serotonin) to an MAOI could improve mood in nondepressed subjects and induce greater improvement in depressed subjects treated with an MAO (44). The influential *permissive hypothesis* of serotonergic function (45) asserted that low central serotonergic function was present in both mania and depression, thus "permitting" a mood disturbance to occur, the form of which was determined by overactivity (mania) or underactivity (depression) of noradrenergic systems. Similar to the lowered levels of CSF MHPG in the catecholamine hypothesis, lower levels of 5-hydroxyindoleacetic acid (5-HIAA, the primary metabolite of serotonin) were demonstrated in the CSF of some depressed patients (46,47). However, subsequent work revealed that low CSF 5-HIAA is strongly associated with impulsivity in a variety of conditions, including suicide, violent criminal behavior, and alcoholism, and is thus not specific to major depression (48). Of the 13 serotonin receptor subtypes characterized to date, only the 5HT1a and 5HT2 receptors have thus far demonstrated a significant link to the pathophysiology of depression. Postmortem examination of tissue from the neocortex of depressed patients has shown an increase in postsynaptic 5HT2 receptors, and, less consistently, similar findings for the 5HT1a receptor (49,50). This suggests that these receptors are increased or defective or they are upregulated as a response to low absolute serotonin levels or activity. The main limitation of postmortem studies of the brains of suicide victims is that the biology of suicide is not equivalent to that of depression; it is estimated that 30% of people completing suicide are not depressed at the time of death (51,52).

More consistent findings have emerged from the study of serotonin uptake in platelets of depressed patients. Platelets are considered a good model for state-dependent brain serotonergic function as they express 5HT2 receptors and take up serotonin via the serotonin reuptake transporter (SERT) in a manner similar to CNS neurons (53). Most studies have found SERT density to be reduced in platelets of depressed patients, though one large study did not find a difference between depressed subjects and controls (54,55). Reduced SERT density has also been found in the cortex and midbrain of depressed subjects (56,57). The interpretation of these older findings may need to be reconsidered in light of the recently identified polymorphism in the promoter region of the SERT gene (SS vs. LL). In general, depressed subjects show blunted prolactin release in response to administration of fenfluramine and L-tryptophan compared with controls, indicating diminished integrity of the serotonin system (58). Some studies have demonstrated that this finding may persist in remitted patients, suggesting that the impaired serotonergic function is a trait, rather than state related (59). The strong preclinical and clinical data demonstrating a role for serotonin in the pathophysiology of depression have led to the targeted development of selective serotonin reuptake inhibitors (SSRIs) as antidepressants.

Unlike the diffuse projection pathways of the serotonin and norepinephrine systems, dopamine transmission in the brain is limited to four discrete paths. The nigrostriatal system projects from the substantia nigra in the midbrain to the basal ganglia, regulating motor control and some components of

cognition, particularly those involved in the cortico-striatal-pallido-thalamo-cortical neuron loops. A second pathway important for reward, emotional expression, and learning is the mesolimbic pathway, projecting from the VTA in the midbrain to the nucleus accumbens, amygdala, hippocampus, and cingulate cortex. The third pathway, the mesocortical, also arises from the VTA and projects to the orbitofrontal and prefrontal cortex, regulating cognitive and emotional response processing. Finally, the tuberoinfundibular pathway projects from the hypothalamus to the pituitary gland, where it inhibits the release of prolactin. The depressive symptoms of psychomotor slowing (nigrostriatal), impaired concentration (mesocortical), and anhedonia (mesolimbic) provide a compelling basis for considering dopaminergic dysfunction in depression. Although reserpine depletes dopamine similar to norepinephrine and serotonin, and MAO catabolizes dopamine similar to the other monoamines, it was not until the 1970s that a role for dopamine in depression was postulated. The effects of cocaine and amphetamine, which block dopamine reuptake and can induce dopamine release, provided the first evidence that enhanced dopaminergic signaling could improve mood. Some antidepressants are thought to act primarily through inhibiting dopamine reuptake, such as bupropion, amineptine, and nomifensine (no longer on the market in the United States). More recently, the efficacy of pramipexole, a D2/D3 receptor agonist, has been demonstrated in small studies of both unipolar and bipolar depressed patients (60,61). Treatment of refractory patients has demonstrated lower concentrations than controls of the dopamine metabolite homovanillic acid (HVA) measured in internal jugular vein samples, with depression severity inversely related to HVA level (62). Interestingly, severely depressed and currently medication-free patients show a significantly greater hedonic response to orally administered amphetamine than do mildly depressed or control subjects (63). Successful chronic antidepressant treatment in humans has been associated with increased D3 gene expression in the shell of nucleus accumbens and increased D2 receptor density in the anterior cingulate cortex and striatum (64,65).

Lower levels of serum dopamine β-hydroxylase (which converts dopamine to norepinephrine) is the only component of the dopamine system that has been found to differ consistently between depressed and control subjects, with this finding limited to patients with psychotic depression (66,67). This suggests involvement of dopamine system in patients with severe or psychotic depression.

There is a rapid (within hours) change in monoamine signaling induced by administration of antidepressants, but there is at least a two- to four-week delay in treatment response to these agents. It is possible that the acute increases in transmitter synaptic concentrations induced by these drugs lead to an increase in feedback inhibition signals through presynaptic autoreceptors, resulting in more gradual changes in signal transmission (68,69). The number and sensitivity of postsynaptic 5HT1a receptors have been shown to increase after effective antidepressant treatment, and animal models demonstrate increased serotonin levels after chronic exposure to antidepressants (70,71). The response of 5HT2 receptors to treatment is less clear, with antidepressant medication inducing their downregulation, but ECT resulting in an increase in their expression (71). The salient effects of antidepressant treatment on monoamine signaling seem to be increased postsynaptic 5HT1a sensitivity and reduced postsynaptic β-receptor, perhaps through 5HT1a autoreceptor desensitization and/or α-2 autoreceptor desensitization (40).

Response to treatment with serotonin- or norepinephrine reuptake–inhibiting drugs appears to be dependent on the availability of the specific neurotransmitter targeted by the drug. Thus, dietary depletion of tryptophan (the amino acid precursor of serotonin) induces depressive relapse in the majority of patients treated with SSRIs, but not those treated with TCAs (72). Similarly, administration of α-methylparatyrosine (AMPT), which reduces levels of catecholamines by inhibiting the action of tyrosine hydroxylase, induces a return of depressive symptoms in patients treated with a TCA, but not with an SSRI (73). In healthy subjects depletion of these monoamine precursors does not lead to depression. Thus, monoamine levels do not seem to have a prime etiological role in the development of depression, but rather serve an important role in modulating other neurobiological systems involved in recovery from depression.

The vast majority of synaptic signaling in the brain occurs via the effects of fast-acting neurotransmitters. Monoamine transmission is thought to exert its effects largely through its relatively slow modulation of the activity of these fast neurotransmitters. γ-Aminobutyric acid (GABA) is the predominant inhibitory neurotransmitter in the CNS, with GABAergic neurons constituting 20% to 40% of all neurons in the cortex and more than three-quarters of all striatal neurons (74,75). Most GABAergic cells in the brain are interneurons (76). Glutamate functions as the main excitatory transmitter of pyramidal neurons (77).

In animal studies involving treatment with antidepressants or electric shock, GABA receptor density is increased by antidepressants (78). Direct GABA injection into rodent hippocampus prevents the development of learned helplessness in rats (79). In humans, CSF and plasma GABA concentrations have been demonstrated to be lower in depressed patients than in controls, with persistence of low plasma GABA levels up to four years after remission, suggesting that low plasma GABA levels may be a trait marker for depression (80). Recent studies employing magnetic resonance spectroscopy found reduced GABA levels in the occipital cortex of depressed subjects compared with controls, with increases in concentrations after successful treatment with medication or ECT (81,82). However, reduction in GABA concentrations is not specific to depression, having also been demonstrated in alcohol dependence and mania (83).

The neurosteroids 3α, 5α-tetrahydroprogesterone (THP, allopregnanolone) and 3α, 5α-tetrahydrodeoxycorticosterone (THDOC) have recently emerged as possible factors in the pathophysiology of major depression. Allopregnanolone can stimulate negative feedback on the hypothalamic-pituitary-adrenal (HPA) axis, as demonstrated by its ability to decrease plasma adrenocorticotropin hormone (ACTH) concentrations and corticotropin-releasing hormone (CRH) release (84,85). In preliminary studies, depressed patients have shown significantly lower serum and CSF allopregnanolone levels compared with healthy controls, with normalization of these concentrations after successful treatment with medications, though not with ECT or transcranial magnetic stimulation (TMS) (86,87). These discrepant results suggest that changes in neuroactive steroid levels following antidepressant therapy may reflect specific pharmacological properties of the medication rather than crucial changes in the biology of the depressed state.

In depression, the *N*-methyl-D-aspartate (NMDA) receptor has been found to be of particular importance. NMDA signaling is crucial to many forms of learning, although high concentrations of glutamate can induce neurotoxicity. Chronic treatment with antidepressants has also been shown to modulate NMDA

receptor function (88). Elevated glutamate levels have been demonstrated in cortical regions where GABA levels are decreased, suggesting that both fast-acting neurotransmitter systems contribute to the pathophysiology of major depression. This finding also raises the possibility that a metabolic pathway common to both systems may be a primary site of dysfunction in MDD (89).

A relatively simple type of receptor is the ligand-gated ion channel (e.g., the GABA-A receptor), which undergoes a conformational change after binding a neurotransmitter, resulting in the passage ions (e.g., chloride) to hyperpolarize (deactivate) the cell. However, other receptors that bind neurotransmitters function by activating a cascade of intracellular events. Many of these receptors are linked to G-proteins on the cytosolic surface of the plasma membrane, which activate second messenger systems, such as cyclic adenosine monophosphate (cAMP), inositol triphosphate, or nitric oxide. Other types of receptors are coupled to tyrosine kinases, which add a phosphate to intracellular proteins, leading to a chain of events resulting in modifications of gene transcription and possible production of essential neuronal proteins (i.e., neurotrophic factors).

The neurotrophic hypothesis proposes that deficient neurotrophic activity contributes to disrupted functioning of the hippocampus in depression and that recovery with antidepressant treatment is mediated in part by reversal of this deficit. The neurotrophins are a family of molecules, including brain-derived neurotrophic factor (BDNF), involved in the maintenance, growth, and survival of neurons and their synapses. cAMP response element–binding protein (CREB) is a protein activated via G-protein systems that increases the expression of neurotrophic and neuroprotective proteins. BDNF also regulates synaptic plasticity through its effects on the NMDA receptor, thus significantly affecting how networks of neurons form, solidify, and communicate (90). Direct injection of BDNF into the rat brain has demonstrated efficacy in two animal models of depression (91,92). Many antidepressants have been shown to increase CREB activity and BDNF levels in the hippocampus and prefrontal cortex, which occurs two to three weeks after initiating the antidepressant, consistent with the usual time course for clinical improvement (93,94). ECT has also been shown to raise BDNF levels in the hippocampus (95).

The frequent observation that depressive episodes emerge in the wake of significant stressor provides the initial impetus for research on the stress axis. The mobilization of bodily resources in the face of threat involved in the stress response is mediated by glucocorticoids (GRs) released from the adrenal cortex. The HPA stress response is a negative feedback system with a starting point in the paraventricular nucleus (PVN) of the hypothalamus. The PVN produces CRH, sometimes referred to as corticotropin-releasing factor (CRF). In conjunction with arginine vasopressin (AVP), also released from the PVN, CRH induces the anterior pituitary to synthesize and release pro-opiomelanocortin (POMC)-derived peptides, including ACTH, and endorphins (endogenous opiods). The ACTH released into the peripheral circulation then moves to the adrenal cortex to stimulate the release of cortisol from the adrenal cortex. Cortisol is the primary effector molecule of the HPA axis, inducing a variety of clinical effects seen in the stress response. In healthy individuals, cortisol induces negative feedback on its own release through interaction with corticosteroid receptors in the pituitary, hypothalamus, hippocampus, amygdala, and septum. Thus, the system seems to have developed to provide the organism with rapid, short-lived responses to acutely threatening situations.

There are two types of these corticosteroid receptors, type I (mineralocorticoid, MR) and type II (GR). MR is thought to mediate the effects of cortisol under low-stress conditions, when the cortisol level is low. As cortisol levels increase, as happens as part of the circadian rhythm or in the face of stress, the MRs saturate, and cortisol signaling occurs through GRs, inducing the negative feedback signal. Once bound with cortisol, both types of corticosteroid receptors translocate to the nucleus, where they act to induce changes in gene expression (96). These changes may lead to other neuronal changes, which may lead to depression.

In Cushing's disease, the presentation mimics depression symptoms, and the levels of cortisol are elevated in the CSF, plasma, and urine of depressed patients. The correlations are particularly strong among the most severely depressed subjects, especially those with psychotic features. Depressed patients tended not to show the same degree of decline in cortisol levels through the day as healthy control subjects, suggesting ongoing inappropriate activity of the cortisol stress response system (97). This observation led to the development of the Dexamethasone Suppression Test (DST), which is typically conducted by administering an oral dose of 1.0 or 1.5 mg of dexamethasone at 11 p.m., followed by plasma cortisol measurements at various times the following day. Individuals with normal function of their HPA axis should significantly suppress (lower) their endogenous cortisol production in response to dexamethasone, due to its negative feedback effects. In MDD, there is often a failure to suppress cortisol production; such subjects are referred to as "nonsuppressors." Unfortunately, the DST has been found to have sensitivity too low for use as a screening test (98). Depressed subjects demonstrating nonsuppression on the DST usually become suppressors after recovery from depression, so the DST may play a role in prediction of depressive relapse (99). A modification to improve the sensitivity of the DST has been to intravenously administer 100 μg of CRH on the day following the dexamethasone dose, so as to further examine dysregulation of the HPA axis. This dexamethasone/CRH test has now become the standard challenge test for HPA functioning in depression (100).

In animal models, chronic stress or exogenous GR administration induces a reduction in the expression of postsynaptic 5HT1a and 5HT1b receptors in the hippocampus. These changes are prevented by chronic antidepressant treatment (101). Reduced signaling through the 5HT1a receptor in the hippocampus may underlie the impaired HPA inhibitory feedback in depression, resulting in the sustained overactivity of the HPA axis (102). GRs can increase levels of tyrosine hydroxylase, resulting in greater catecholamine production, thus linking the findings of both greater dopaminergic signaling and elevated HPA axis activity in psychotic versus nonpsychotic depressed subjects (103). Elevated CRH levels in CSF of depressed patients have been repeatedly demonstrated, with normalization of these levels with successful treatment (104). Intravenous administration of CRH produces blunted ACTH and endorphin release in depressed subjects compared with controls, suggesting that chronic oversecretion of CRH results in downregulation of CRH receptors in the pituitary (105). Oversecretion of CRH may stem from the finding of increased numbers of CRH-containing cells in the PVN in subjects with depression (106). Even though there is blunted responsiveness of ACTH release to CRH stimulation, overall cortisol levels remain elevated, probably secondary to the hypertrophy of the adrenal cortex

that occurs in depression. Centrally administered CRH, severe depression, and the stress response all induce a similar symptom profile of reduced sleep, appetite, and sexual behavior, increased heart rate and blood pressure, and altered motor activity (107).

The overall picture that emerges is one of failure of HPA feedback mechanisms to terminate the stress response in patients with major depression. Instead of a short-lived activation in face of an acute threat, the HPA axis continues to function as if the stress or threat was ongoing, resulting in chronic maladaptive changes.

In the *stress-diathesis hypothesis* of depression, childhood abuse or neglect and loss of a parent are considered to constitute an early life stress (ELS). The increased risk for depression (and anxiety disorders) among adults who experienced ELS is well established (108,109). Genetic inheritance may play a role in the vulnerability of developing depression, such as inheriting the SS allele of the SERT.

In animal studies, rat pups exposed to maternal deprivation display hypersecretion of CRH and increased CRH signal transduction and abnormal functioning of both norepinephrine and serotonin systems in adulthood when exposed to psychological stressors as adults (110,111). Treatment with an SSRI or cross-foster parenting the rats results in improvement in these factors. Retrospective studies of adults who experienced ELS have identified exaggerated levels of HPA activity when under stress (112). A recent groundbreaking study by Heim and colleagues examined HPA axis response to social stress in women with or without ELS exposure and with or without current major depression (113). Only women with a history of ELS demonstrated increased plasma ACTH and cortisol response to the stressor, and women with both ELS and depression had a sixfold greater ACTH response to stress compared with non-ELS, nondepressed control subjects. While much work remains to be done to clarify the neurobiological consequences of ELS, these data suggest that there may be a permanent change in the set point for HPA activity in the face of stress among people exposed to ELS, perhaps forming the biological basis for a subtype of depression.

The hypothalamic-pituitary-thyroid (HPT) axis is organized similar to the HPA axis, with thyrotropin-releasing hormone (TRH) released from the median eminence of the hypothalamus, which travels through the hypothalamo-hypophyseal portal system to induce the release of thyroid-stimulating hormone (TSH) from the anterior pituitary into the peripheral circulation. TSH then induces the synthesis and release of the thyroid hormones, tri-iodothyronine (T3) and thyroxine (T4). T3 and T4 provide negative feedback at the hypothalamus and pituitary gland to inhibit the release of further TRH and TSH, thus reducing activity of the axis. T4 present in the brain is converted to T3, (considered the active form of thyroid hormone in the CNS). The action of this enzyme can be inhibited by cortisol, thus linking the HPT and HPA axes in depression (114). Paralleling the findings of elevated CRH function in depression, the levels of TRH in CSF have been found to be higher in depressed subjects than in healthy controls (115). TSH release in response to intravenous TRH stimulation has been demonstrated to be blunted in a minority of patients with major depression (116). On the other hand, about 15% of patients with major depression display supersensitive TSH response to TRH stimulation (117). The HPT axis can also be disrupted by two antithyroid antibodies, antithyroglobulin and antithyroid microsomal antibodies. These antibodies are found more frequently in depressed subjects than the general population (118). While

severe thyroid dysfunction is one path by which a depressive syndrome can be induced, the contribution of milder, subclinical forms of thyroid dysfunction to depressive symptomatology is less clear. Aside from the question of pathophysiology, it is likely that MDD in the presence of thyroid dysfunction results in poorer response to treatment.

GH is secreted from the anterior pituitary and may have a role in depression through its effects on the homeostasis of body fuel stores. Two hypothalamic peptides control secretion of GH: somatostatin inhibits and GHRH stimulates GH release. Dopamine, norepinephrine, and tryptophan also stimulate GH secretion. In healthy adults, GH secretion follows a circadian pattern, with peak levels in the first few hours of sleep. Depressed subjects, however, show diminished nocturnal GH release and higher daylight GH levels (119,120). Adolescents demonstrating lower levels of GH release prior to sleep onset demonstrate greater risk of developing depression as adults (121). Response to clonidine, a centrally acting α-2 agonist, which normally stimulates GH release, is blunted in depressed patients (39).

Somatostatin is produced in the hypothalamus and has inhibitory effects on GABA activity and the release of GH, CRH, ACTH, and TRH. This neuropeptide is therefore positioned to influence many of the factors implicated in the pathophysiology of depression. Several studies have demonstrated reduced levels of somatostatin in the CSF of depressed patients, which may stem from GR inhibition of somatostatin neurons (122,123).

Sleep is also of significance in depression in that sleep disruption can occur as part of the prodrome to a MDE, as a symptom during the episode, or linger as a residual symptom in patients remitted from their illness. Depressed patients show three major changes in sleep pattern: reduced sleep maintenance, reduced latency to first episode of rapid eye movement (REM) sleep, and diminished slow wave sleep (SWS, delta, or stages 3 and 4 sleep) (124). The latter two features often persist after achieving remission from the depressive episode. Theories about the pathophysiological relationship between sleep and depression have focused on REM sleep disturbances, supported by the finding that most antidepressants suppress REM sleep (124). Also, loss of SWS leads to loss of GH, which has been commented on earlier. REM sleep occurs during periods of cholinergic activation, which is usually inhibited by serotonergic projections to the cholinergic nuclei in the pons. Thus, an imbalance of monoamine/cholinergic function, such as decreased serotonergic transmission or increased cholinergic activity or sensitivity, can reduce SWS and increase REM sleep. REM suppression with antidepressant treatment may result from increased postsynaptic 5HT1a receptor activity or increased transmission of catecholamines (125). Recent work has also demonstrated abnormal brain activity in the period prior to the onset of non-REM sleep in depressed patients. During the transition from wakefulness to non-REM sleep, depressed subjects show greater persistence of waking-state levels of high metabolic activity in the thalamus and frontal and parietal cortical regions compared with controls (126). These may result in the subjective complaints of insomnia and nonrestorative sleep reported by depressed patients.

The overexpression of proinflammatory cytokines may contribute to the pathophysiology of depression, which has led to the *macrophage hypothesis* of depression (127). Many patients who receive interferon-α (a cytokine used to treat hepatitis C and melanoma) or interleukin (IL)-2 develop depressive

syndromes, and these symptoms of depression can be prevented and treated by standard antidepressant regimens (128,129). A positive relationship between severity of depression and serum levels of cytokines has been demonstrated (130). Antidepressants exhibit anti-inflammatory activity, with clinical response correlated with reductions in cytokine levels (131). Finally, an IL-1 receptor antagonist has been shown to prevent the development of learned helplessness in rats (132). Women display higher immune activation levels than men, and experience a spike in secretion of cytokines with childbirth, providing a possible biological basis for the higher incidence of MDD in women (133,134).

Elevated cytokine activity may also provide a link to the epidemiological link between depression and increased rates of death after heart attack (135).

CONCLUSIONS

Despite MDD's position as a leading public health problem worldwide, our understanding of the etiology and pathophysiology of the illness has been remarkably limited. Now, however, previously segregated approaches to exploring depression along the lines of monoamine functioning, neuroendocrine alterations, and psychological measures are becoming increasingly integrated. With the advancements of research methodologies in genetics, cell biology, and neuroimaging, a more comprehensive model of depression is taking the place of the older system-bound theories. Although we lack a definitive theory, several components of neurobiology discussed in this chapter are certain to have relevance to the etiology and pathophysiology of MDD. The genetic inheritance of the individual provides the basic components conveying vulnerability or resilience to the development of the illness. The rearing environment further modifies these characteristics, setting the stage for the potential of developing a mood disorder in adulthood. Later psychological and social stressors may initiate cascades of events via the stress response system, affecting other neuroendocrine systems, monoamine activity, and the functioning of intracellular signaling pathways, such as CREB regulation of BDNF. This disruption of neurotrophin function in maintaining neuronal and synaptic integrity, particularly in the hippocampus, may lead to the disruptions of connectivity between brain regions identified in the neuroimaging studies of depressed subjects. This dysfunctional brain circuitry reveals itself in the symptoms of depression seen in the clinic, with phenotypic variability between individuals potentially stemming from the specificity and degree of circuit disruption. While this model is complex, and sure to become even more complicated with the findings of future studies, it reflects the intricacy of the organ that forms the basis of our conscious experience.

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2 Outcomes in the Treatment of Major Depressive Disorder

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INTRODUCTION

Major depressive disorder (MDD) is one of the world's greatest public health problems (1), and in industrialized nations, it is the leading cause of disability (2). Theoretical and clinical approaches to the treatment of depression have changed greatly since the psychoanalytic models of treatment dominated the psychiatric landscape in the mid-20th century. Seminal developments in the 1950s and 1960s included recognition that several distinctly different types of medication had antidepressant effects, which ultimately shaped the influential monoamine hypotheses of depression and helped to define treatment for the decades to come. Concurrently, the pioneering work of Beck (cognitive therapy; CT), Klerman and Weisman (interpersonal psychotherapy; IPT), and other psychotherapy researchers led to the introduction of several time-limited, operationalized forms of psychosocial intervention specifically developed to treat depression. As understanding of the etiology, pathophysiology, and risk factors of MDD continued to grow over the next three decades, additional pharmacological and psychosocial therapies have been introduced. This chapter is designed to provide a framework to help understand the contemporary biopsychosocial approach to treatment of depressive disorders, including brief reviews of the current evidence base that guides the acute and longer-term phases of treatment.

RANDOMIZED CONTROLLED TRIALS AND SIGNAL DETECTION

Before embarking on a discussion of particular treatment strategies, it may be useful to briefly examine the methodology used to assess the efficacy of the various treatments for depression. For over 40 years, the randomized controlled trial (RCT) has been the criterion standard for evaluation of medical therapies. The major strengths of RCTs are that random assignment helps to ensure that the treatment groups being compared are comparable, use of standardized protocols helps to ensure that the experiment is replicable, and inclusion of one or more comparison groups provides the context for assessing the impact of the intervention (i.e., "compared with what?") (3). For pharmacotherapy studies, a double-blind, placebo-controlled group is the optimal means to determine treatment efficacy; the outcome of the placebo control group reflects the impact of all factors except those directly resulting from the pharmacological effects of the medication. There is not an ideal analogue for a placebo in studies of psychosocial interventions (i.e., a pseudotherapy does not really function as a placebo if the clinician providing the intervention knows that it is a "dud"), so investigators sometimes use a waiting-list or assessment-only control group in early studies and a three-arm design (i.e., psychotherapy, active drug, and

placebo) for more advanced studies. The major inherent limitation of RCTs is that the study protocol—including various inclusion and exclusion criteria that may rule out a large majority of depressed people seeking treatment—limits generalizability to the patients seen in everyday clinical practice. For this reason, two types of RCTs are now recommended: an initial series of highly controlled studies to establish whether or not the treatment works (i.e., *efficacy* research designs, which emphasize the internal validity of the experiment), followed by larger, more inclusive studies conducted in "real-world" settings (i.e., *effectiveness* research designs, which emphasize generalizability).

The impact of various forms of acute phase therapy for depression should be apparent within a few months. Studies of the initial or acute phase of treatment thus typically last from 4 to 8 weeks for pharmacotherapy and from 8 to 16 weeks for psychotherapy. The traditional outcome of interest has been termed *response*, which commonly has been defined by at least a 50% reduction in symptom burden (4). Most—albeit not all—individuals who experience at least a 50% reduction in symptom intensity will no longer meet the criteria for a major depressive episode and will perceive qualitative improvement. A number of reliable and validated assessment scales are available to quantify symptom burden, including older standards such as the Hamilton Rating Scale for Depression (HAM-D) (5), the Montgomery Asberg Depression Rating Scale (MADRS) (6), and the Beck Depression Inventory (BDI) (7) and newer measures such as the depression subscale of the Patient Health Questionnaire (PHQ-9) (8) and inventory of depressive symptomatology (IDS) (9). Clinician-administered rating scales are rarely used in day-to-day practice, and for this purpose self-administered scales such as the BDI and PHQ are ideal. An abbreviated, self-report version of the IDS, known as the quick inventory of depressive symptomatology - self report (QIDS-SR) (10), has the additional advantage of being in the public domain, which means that it can be administered without cost.

More recently, both investigators and clinicians have begun to use the more restrictive term *remission* to describe treatment success (11,12). Remission describes a virtually complete relief of depressive symptoms, such that the person who has remitted would have a level of symptom burden that would be essentially indistinguishable from someone who has never been depressed (4,13). Remission should be thought of as the "gateway" to recovery (i.e., a period of sustained remission, lasting at least two months or longer). Remission also is a necessary, though not necessarily sufficient, state for resolution of the psychosocial and vocational impairments that were associated with the depressive episode. In practice, however, it sometimes takes months or even years for normalization of functional status (14). So defined, the construct of remission is now well validated, and people who "respond" but do not remit have been found to have a higher risk of subsequent relapse (15–17) and poorer social and vocational functioning (18). Specific symptom severity scores to define remission have been validated for each of the commonly used rating scales (e.g., a HAM-D score of $\leq$7, a MADRS score of $\leq$10, or a QIDS-SR score of $\leq$5) (10,19). The major advantage of using remission—rather than response—to define a successful outcome in treatment research studies is that a larger amount of improvement is required, which increases certainty that the patients who are said to have benefited from the intervention have truly had a good outcome.

There has recently been some controversy regarding the effectiveness of antidepressants (20–22). Results of the early clinical trials of antidepressants in

the 1960s shaped the expectation that an effective medication can be expected to deliver a response rate of approximately 67%, as compared with a placebo response rate of around 33% (see the detailed review in Ref. 23). The advantage for the active drug in this scenario is large, whether expressed as an absolute value (i.e., a 34% "rate difference"), a relative benefit (i.e., 100% or twofold advantage), an odds ratio (OR = 4.1), or as the number needed to treat for benefit (NNT = 2). The effect of treatment can also be described by computing standardized difference scores or effect sizes (abbreviated as *d*) on measures such as the HAM-D or MADRS, which are most commonly calculated by dividing the difference score between the active treatment and placebo by the pooled standard deviation (24). In the scenario described above, a 33% advantage in response rate corresponds to about a six-point difference on the HAM-D. As the standard deviation of the HAM-D at posttreatment is usually about 10 points, *d* would equal about 0.6.

It is not difficult to detect large effects in RCTs, and in the studies conducted in the 1960s or 1970s, investigators only needed to enroll about 30 to 50 patients per arm to have an acceptable level of statistical power (i.e., at least an 80% chance of obtaining a statistically significant finding). The situation in 2009 is much different, however, and there is strong evidence that the effect sizes observed in placebo-controlled studies of antidepressants have grown progressively smaller across the past 30 years (21). In fact, average drug versus placebo differences in response rates more typically range from 10% to 15% in contemporary studies, with NNT values ranging from 7 to 10 and effect sizes on the order of $d = 0.3$ or 0.4. Differences of this magnitude are judged to be relatively small effects and are on the margin of what can be considered to be clinically significant (25).

In an era in which such modest drug-placebo differences are the norm, investigators must plan to enroll much larger sample sizes to maintain acceptable statistical power. Indeed, a study would need to be quite large—on the order of 300 patients per arm—to have adequate statistical power to detect a 10% difference in response rates (3). As few studies enroll more than 150 patients per arm, it should come as no surprise that about one half of contemporary studies fail to detect significant differences between antidepressants with proven efficacy and placebo. Statisticians refer to this type of outcome as a type-2 error (i.e., the failure to confirm a statistically significant difference because of inadequate power) and the high rate of type-2 errors is emblematic of a loss of signal detection or decreased "assay sensitivity" (21). Although there are a number of reasons for this secular trend, a steady increase in the average placebo response rate across the past 30 years (26) accounts for at least part of the problem. As the chemical composition of placebo has not changed, the growing placebo response rate no doubt reflects both higher expectations of benefit and changes in the populations of depressed people who enroll in clinical trials (e.g., a shift to less severely or pervasively ill study participants).

The difficulty in signal detection in placebo-controlled studies also extends to comparisons between active antidepressant medications or between a psychotherapy and an antidepressant. Specifically, the drug versus placebo difference may be thought of as the upward boundary of signal detection, and it is proportionally more difficult to discern a difference between two effective therapies than to find an effect between an active therapy and a placebo (3). Thus, unless adequately powered to find modest between-group differences,

comparative studies are essentially destined to find that there are no significant differences between therapies. It is even more difficult to test "noninferiority" (to confirm with a high degree of certainty that two treatments have equivalent effects); noninferiority studies typically need to enroll at least three times as many subjects as a study designed to determine if treatment A is superior to treatment B. The field therefore has been stymied by the inability to differentiate between therapies that are truly comparable (in statistical terms, treatment A would be noninferior to treatment B with a high degree of certainty) and those that may have modest, but still clinically meaningful differences (21).

Given a dearth of definitive, large-scale comparative studies, some researchers use statistical approaches collectively called meta-analysis to synthesize data from available smaller studies. Two principal types of meta-analyses exist. The first draws from summary data extracted from published papers, abstracts, and study reports. In this scenario, *N* is the number of trials, and the dependent variable is either categorical (such as response rate) or continuous (such as change in HAM-D score). The other type of meta-analysis combines or pools the data (such as scores on validated rating scales, such as the HAM-D) from each participant in a series of studies. In this scenario, raw individual patient data is available, and *N* is the number of study participants. Because source data is available, a better range of outcomes can be examined using this second method. The meta-analysis of summary data is more widely used, however, which is due in large part to the fact that individual subject data are usually not available.

Although meta-analysis is superior to impressionistic or narrative review of a group of studies, this approach to data synthesis is far from foolproof and is subject to several potential biases. Most important is the so-called "file drawer effect," which refers to the fact that failed or negative studies are much more likely to be unpublished than studies that yield statistically significant results. A meta-analysis that is limited to the published literature is thus likely to overestimate the effect of the treatment, with the magnitude of the bias proportional to the number of studies that have been overlooked. The file drawer effect is particularly relevant to meta-analyses of antidepressant pharmacotherapy, because a large proportion of the studies have been conducted by the pharmaceutical industry and—until recently—the tendency to not publish failed studies has been shown to be pronounced (22). This situation is being rectified, as most companies now post results of all of their studies on Websites and often make more detailed results available upon request for use in meta-analyses. A second problem, sometimes referred to as "mixing apples and oranges," describes a bias that can be introduced when the results of studies that are too dissimilar are combined. Klein (27) illustrated the impact of this bias in earlier meta-analyses that compared the effects of psychotherapy and antidepressants. Specifically, when effect sizes were calculated after pooling studies using different types of control groups (i.e., waiting list vs. placebo) and different durations of treatment (i.e., 12–16 weeks vs. 4–8 weeks), the bias favored the psychotherapies because the studies were more likely to use the weaker control group (the waiting list) and tended to be of longer duration than the pharmacotherapy studies. To avoid this bias, it is wise to limit meta-analyses to studies that directly compare the strategies of interest.

ACUTE PHASE PHARMACOTHERAPY

The acute phase of antidepressant treatment begins with the initiation of treatment and should continue until the patient has had a successful outcome (28). Pharmacotherapy visits typically last between 15 and 30 minutes and should include symptom assessment, psychoeducation, and supportive clinical management (29). Patients are typically seen weekly or every other week during the acute phase of pharmacotherapy. As noted previously, monitoring of treatment outcome is facilitated by use of a standardized assessment scale, with preference given to self-report measures because they can be filled out by the patient before the clinical visit. Although it is always hoped that the first choice of treatment will be effective, as often as not a second treatment trial will be needed, and a not insignificant proportion of patients will require three or more treatment trials. Perhaps as many as 20% of patients will obtain little benefit from four or more treatment trials (30).

The treatment of first choice for outpatients with nonpsychotic episodes of MDD is largely determined by the patients' selection of providers: those who see counselors or psychologists are more likely to receive a psychosocial intervention, whereas those who see a primary care physician or psychiatrist are more likely to be prescribed an antidepressant medication. Although many consider a treatment plan that includes psychotherapy and pharmacotherapy to be the best approach (29), the advantage for routinely combining modalities is best documented for patients with more severe, chronic, or complex disorders (31). Selection of a particular antidepressant as the treatment of first choice is a function of clinician preference, the patient's past treatment history, and factors such as cost, safety, and tolerability (29).

First-Generation Antidepressants

Prior to 1987 there were essentially two types of antidepressant medications: one named for the chemical structure of the members of the class (the tricyclic antidepressants or TCAs) and the other named for the presumed mechanism of action (the monoamine oxidase inhibitors or MAOIs). Both types of medications are thought to initiate antidepressant effects by potentiating monoamine neurotransmission, with the TCAs primarily exerting this effect by inhibiting norepinephrine uptake at the synaptic cleft and the MAOIs by blocking the intraneuronal degradation of norepinephrine, serotonin, and dopamine.

Although the TCAs and MAOIs have been largely supplanted by the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), the introduction of these drugs more than 50 years ago heralded the modern era of treatment of depressive disorders. As the definition of depression and measurement of depressive symptoms have undergone a number of changes since the introduction of these drugs, we will use meta-analyses to examine the relative efficacy of these agents, both in comparison with each other and with the newer antidepressants. Thase et al. (32) presented a meta-analysis of all published reports comparing the TCAs with MAOIs phenelzine, tranylcypromine, or isocarboxazid. They found that although the MAOIs were more effective than placebo in studies of hospitalized depressed patients, they were significantly less effective than the TCAs. In contrast, they reported trends favoring the MAOIs over the TCAs in the studies of depressed outpatients. Stewart et al. (33) likewise concluded that MAOIs were

superior to TCAs in a meta-analysis of individual patient data from RCTs that enrolled only outpatients with atypical depression (i.e., depressive syndromes characterized by preserved mood reactivity and reverse neurovegetative symptoms). In this meta-analysis, the researchers found that the MAOI was superior to the TCA, which in turn was more effective than placebo in treating this depressive subtype. Thus, the notion that these two classes of antidepressants were equally effective was only true in the broadest sense (i.e., by lumping together studies of inpatients and outpatients, with or without atypical depression).

Although the MAOIs were particularly effective antidepressants for one subset of depressed people, the vast majority of clinicians strongly favored the TCAs for first-line therapy. This was because of the risks of drug-drug and dietary interactions during MAOI therapy, particularly the notorious "cheese effect" (i.e., a hypertensive crisis following ingestion of foodstuffs rich in the amino acid tyramine). Attempts to develop safer MAOIs are ongoing, and several newer MAOIs are available, including transdermally delivered seligiline (34) and, outside of the United States, moclobemide, which is a reversible inhibitor of the MAO-A isoenzyme. Despite some improvements over the older, nonselective/irreversible drugs, neither of the newer MAOIs is widely used, with concerns about efficacy limiting use of moclobemide (35) and cost and the need for the low tyramine diet (at higher doses) limiting enthusiasm for the seligiline skin patch (36).

Although many newer antidepressants have been introduced over the past two decades, most belong to two classes, the SSRIs or the SNRIs. With only a few exceptions, these "newer" antidepressants are now available in generic formulations. The SSRIs, SNRIs, and other newer antidepressants are generally no more effective than the TCAs and MAOIs, but they do have certain advantages, including less need for titration, more favorable tolerability profiles, and lower risks of toxicity following overdose (29,36).

Selective Serotonin Reuptake Inhibitors

At the forefront of the second generation of antidepressants were the SSRIs, which are related to one another by the common chemical profile that they share—namely, the potent and relatively selective inhibition of the 5HT uptake transporter. The selectivity of action largely underpins the tolerability advantage of the SSRIs compared with the TCAs, for which many of the side effects are mediated by blockade of cholinergic, histaminergic, and adrenergic receptors (37). The SSRIs also have a substantial advantage in terms of safety following overdose compared with the TCAs (38), which is accounted for by a lack of effect on cardiac conduction.

The SSRI class includes five distinct antidepressants: fluoxetine, fluvoxamine, sertraline, paroxetine, and citalopram. A sixth SSRI, escitalopram, is the active (S) stereoisomer of citalopram. In terms of efficacy and tolerability versus the TCAs, scores of RCTs have been conducted and a number of meta-analyses have been performed (39–41). As noted earlier, interpretation of these data must be accompanied by the caveat that most of the RCTs were conducted by the manufacturers of the SSRIs, and as a result, it is likely that at least some relevant studies with results favoring the TCAs were not published. It is also true that the SSRIs are somewhat easier to dose than the TCAs, which require slow upward

titration over several weeks. As a result, it is likely that a number of these RCTs used titration protocols that underestimated the therapeutic potential of the TCAs. Nevertheless, it can be said with reasonable certainty that the major advantage favoring the SSRIs over the TCAs in clinical trials is better tolerability. For example, Montgomery et al. (42) reported that 27% of patients discontinued TCAs because of adverse side effects, compared with 19% of patients receiving SSRIs in a meta-analysis of 42 RCTs. In certain subpopulations of depressed patients, such as the elderly, this tolerability advantage is even more profound. For example, in a 12-week study of 116 depressed elders, Roose et al. (43) found that the rate of discontinuation due to side effects in individuals treated with the TCA nortriptyline was double that of those treated with the SSRI paroxetine (33% vs. 16%).

Although meta-analyses have generally found that the SSRIs and TCAs have comparable efficacy, there is some evidence to suggest that the TCAs are more effective than the SSRIs for treatment of severe depression. For example, in a meta-analysis of 25 inpatient studies, Anderson (44) found a large advantage for the TCAs, which in turn was almost entirely explained by the results of the studies of just two of the TCAs, amitriptyline and clomipramine. In other words, the meta-analysis of inpatient studies that compared SSRIs with other TCAs (imipramine, desipramine, nortriptyline, and the closely related tetracyclic compound maprotiline) failed to detect any meaningful difference between the classes of antidepressants. The most likely reason for this difference is that whereas imipramine, desipramine, nortriptyline, and maprotiline are primarily norepinephrine reuptake inhibitors, amitriptyline and clomipramine also impact serotonin neurotransmission. This observation helped to form the basis for the "dual reuptake inhibition" hypothesis, which posits that medications that enhance both serotoninergic and noradrenergic neurotransmission will exert stronger antidepressant effects than those that selectively affect only norepinephrine or serotonin systems.

With respect to the SSRI class, no one compound has emerged as inherently superior to the others (36,37). Currently, most health care systems that use pharmacy benefit plans favor prescription of the SSRIs that are generically available (in the United States: citalopram, fluoxetine, paroxetine, and sertraline) over escitalopram simply because of the difference in acquisition cost. The SSRIs are not truly interchangeable, however, and there are certain pharmacokinetic and pharmacodynamic differences between the various members of the class, which account for some differences in tolerability and risk of discontinuation symptoms following abrupt discontinuation (36,37). The therapeutic effects of fluoxetine, for example, tend to emerge more slowly than those of some of the other SSRIs (25,37). The most likely explanation for this difference is that both fluoxetine and its principal metabolite—norfluoxetine—have long elimination half-lives, which result in a much slower time to steady-state plasma levels when compared with the other SSRIs. The extremely long elimination half-life of norfluoxetine also helps to explain why fluoxetine therapy is associated with the lowest incidence of discontinuation symptoms (45). Another difference between a particular pair of SSRIs is that escitalopram appears to have a disproportionately stronger antidepressant effect than its racemic parent drug, citalopram (46). This difference may be explained by the effects of the inactive stereoisomer, *R*-citalopram, which may antagonize the activity of the active S-enantiomer (47). When compared with the other SSRIs, escitalopram has the

advantage of even simpler dosing and has shown greater efficacy in several head-to-head trials (48). Although these potential advantages may be largely negated by a greater acquisition cost (49), it is likely that the relative merits of escitalopram will be reevaluated when it too is available in generic formulations.

Serotonin-Norepinephrine Reuptake Inhibitors

The SNRIs are the second most widely prescribed class of newer antidepressants. This class contains three members in the United States—venlafaxine, desvenlafaxine, and duloxetine—with a fourth (milnacipran) available elsewhere in the world. Introduced after the SSRIs, the SNRIs are often ranked as second-line therapies, partly because of slightly poorer tolerability and largely because most members of the class are still patent protected (36). Similar to clomipramine, the model "dual-acting" TCA, the SNRIs directly modulate serotonin and norepinephrine neurotransmission. Given the data reviewed earlier pertaining to the superiority of the dual-acting TCAs in severe depression and the improved tolerability of the SNRIs compared with the TCAs, it was hoped that the SNRIs would have the potential to become the most useful antidepressants developed to date. The data that have emerged over the past decade have only partly supported this prediction, however, as discussed below (50).

Venlafaxine, which was the first SNRI to be introduced, is the most extensively studied member of the class. While some evidence of an efficacy advantage over fluoxetine has existed since the mid-1990s (51,52), there has not been uniform acceptance of the fact that venlafaxine has greater therapeutic effects than the SSRIs as a class. One reason for this is that venlafaxine and its major metabolite, *O*-desmethylvenlafaxine, are both substantially more potent inhibitors of serotonin uptake transporters than norepinephrine, which has raised concerns that the drug may not be a true "SNRI" at lower therapeutic doses. Moreover, as therapy with the initial formulation of venlafaxine was associated with greater difficulties with dosing titration and a greater incidence of certain adverse effects—a higher incidence of nausea early in the course of therapy and a greater incidence of treatment-emergent high blood pressure—as compared with the SSRIs, venlafaxine was typically reserved for second- or third-line use behind the SSRIs (53). The introduction of an extended-release formulation in 1997 addressed some of these concerns, though the question about the dose at which venlafaxine becomes a dual reuptake inhibitor has largely remained unanswered. This point is particularly important because the antidepressant effects of venlafaxine show some degree of dose dependence (54) and the manufacturer did not obtain FDA approval to use the extended-release formulation in the highest (i.e., 300 and 375 mg/day) doses.

Venlafaxine is one of the most extensively studied of the modern antidepressants, and nearly 50 RCTs comparing it with SSRIs have been completed. A number of meta-analyses have also been performed, including those using study summary results (55,56) and original data sets (57–59). Collectively, these meta-analyses document a modest advantage (i.e., a 5–10% difference in remission rates) favoring venlafaxine over the SSRIs (52,53). The clinical significance of an advantage of this magnitude is debatable, particularly because the extended-release formulation of venlafaxine is not yet available in a generic formulation.

Milnacipran was the second SNRI to come to the international marketplace. In contrast to venlafaxine, milnacipran is a much more potent inhibitor of

norepinephrine uptake, and the threshold at which the drug develops clinically significant serotoninergic effects is not established (57,58). In contrast to venlafaxine, available evidence indicates that milnacipran does not have an efficacy advantage over the SSRIs (60). This finding certainly does not support the "dual reuptake inhibitor" hypothesis, although it may simply be the case that the clinically tolerable doses of milnacipran do not sufficiently inhibit serotonin reuptake to produce the desired effect.

The third SNRI to come to market worldwide was duloxetine. When compared with the other SNRIs, duloxetine has been described as a "balanced SNRI," which refers to the fact that—at least in in vitro studies—duloxetine is a more potent norepinephrine reuptake inhibitor than venlafaxine, and a more potent serotonin reuptake inhibitor than milnacipran (61). If these laboratory findings parallel the in vivo effects of the drug, one would expect that duloxetine would exert a clinically relevant effect on both neuronal systems at a minimal therapeutic dose (i.e., 60 mg), and consistent with this, duloxetine has not been shown to have a dose-response relationship between 60 and 120 mg/day. When compared with venlafaxine, a second potential advantage is that duloxetine has shown less effect on blood pressure (62,63). A report presenting a pooled analysis of a pair of RCTs contrasting duloxetine (60 mg/day) and venlafaxine XR (75–150 mg/day) failed to demonstrate any meaningful efficacy differences between the two SNRIs, though duloxetine therapy was associated with greater tolerability difficulties early in the course of therapy, and venlafaxine XR therapy was associated with greater difficulties with discontinuation of therapy at the end of the 12-week treatment protocol (64).

A meta-analysis of the first six double-blind, placebo-controlled trials using SSRIs as comparators (two with fluoxetine and four with paroxetine) was recently published, and the results provide further, albeit limited, support for the dual reuptake inhibitor hypothesis (65,66). Although the overall difference in efficacy between duloxetine and the SSRIs was not statistically significant, the SNRI did convey about a 10% advantage in remission rates in the subset of patients with moderate to severe depression. Unfortunately, this meta-analysis is flawed by a dosing imbalance: a majority of the duloxetine-treated patients were treated with doses that are above the minimum therapeutic dose (60 mg/day), whereas all of the patients treated with an SSRI received the minimum therapeutic dose (i.e., 20 mg/day of fluoxetine and paroxetine). Three subsequent trials comparing duloxetine (60 mg/day) with escitalopram (20 mg/day) failed to document any efficacy advantage for the SNRI (67–69).

The fourth (and in all likelihood final) member of the SNRI class is desvenlafaxine, which is the succinate salt of *O*-desmethylvenlafaxine (i.e., the principal active metabolite of venlafaxine). The clinical pharmacology of desvenlafaxine differs from the parent drug in three ways: (*i*) it is not metabolized in the liver and plasma drug levels are not affected by individual differences in drug metabolism; (*ii*) the succinate salt formulation conveys substantially more bioavailability than the hydrochloride salt formulation of the parent drug; and (*iii*) desvenlafaxine has greater in vitro potency for inhibition of the norepinephrine uptake transporter (70). The net result of these differences is that the minimum effective dose of desvenlafaxine is relatively low (50 mg/day) and—in contrast to venlafaxine—desvenlafaxine does not appear to show a dose-response relationship.

Other Second-Generation Antidepressants

Bupropion is the most widely used antidepressant that is not classified as an SSRI or SNRI. It is sometimes referred to as a norepinephrine and dopamine reuptake inhibitor (NDRI), although in vivo potency for these actions has not been convincingly established (36). A number of head-to-head RCTs have been conducted that compare bupropion and various SSRIs, with meta-analyses indicating almost exact parity with the SSRIs (62,63,71). The major rationale for selecting bupropion instead of an SSRI or SNRI is that it has a much lower incidence of treatment-emergent sexual side effects (62,63,72). There has been some reluctance to use this nonsedating medication for treatment of patients with prominent anxiety: it is in fact one of the few widely prescribed modern antidepressants with no approved indications for treatment of anxiety disorders. Nevertheless, attempts to establish differential efficacy in analyses of pooled data sets have not demonstrated efficacy differences versus SSRIs, particularly with respect to anxiety associated with depression (71).

Considerable enthusiasm exists for adding bupropion as an adjunct to an incompletely effective SSRI, which in a sense represents clinicians' attempts to fashion an ersatz "triple reuptake inhibitor." Although this strategy did relatively well in the large, National Institute of Mental Health (NIMH)-funded STAR*D trial (73,74), the difference between the combination of citalopram and bupropion and the other "add-on" option (augmentation with the anxiolytic medication buspirone) was not statistically significant. The potential impact of this study was also limited by the fact that statistical comparisons could not be made between bupropion augmentation and the other major strategy tested—switching to a different antidepressant following citalopram nonresponse—because too few patients consented to randomization options that included both switching and augmenting strategies.

Two other second-generation antidepressants—nefazodone and mirtazapine—are also distinct from the SSRI and SNRI classes; these drugs are sometimes referred to as "norepinephrine and serotonin receptor modulators." Nefazodone, which is structurally linked to the older compounds trazodone and buspirone, is a potent $5HT_2$ inhibitor and a weak, transient inhibitor of 5HT and NE uptake (75). The manufacturer of nefazodone conducted a number of head-to-head, nonplacebo comparisons with SSRIs, which in aggregate indicate comparable efficacy (76). Nefazodone has some advantages compared to SSRIs with respect to better effects on sleep (77) and a lower incidence of sexual dysfunction (78). The potential clinical niche for a drug with this profile has been largely negated, however, by emerging concerns about hepatotoxicity, which led to the withdrawal of nefazodone from many countries other than the United States (36).

Mirtazapine, a tetracyclic compound that has virtually no inhibitory effects on any monoamine uptake transporters, is thought to potentiate norepinephrine and serotonin neurotransmission by blocking presynaptic α-2 autoreceptors on norepinephrine neurons, and α-2 heteroreceptors on serotonin neurons; mirtazapine also potently blocks postsynaptic histamine-1, $5HT_2$, and $5HT_3$ receptors (79). As a consequence of this combination of effects, mirtazapine is the most sedating of all the newer antidepressants and is essentially devoid of the common gastrointestinal (i.e., diarrhea, nausea) and sexual side effects that are associated with the serotonin reuptake inhibitors. Mirtazapine does stimulate appetite, however, and approximately 20% of patients treated with this agent will experience a problematic amount of weight gain; this has greatly limited the

use of this medication in patients who do not have significant weight loss as a key depressive symptom (36). A meta-analysis of head-to-head RCTs comparing mirtazapine with the SSRIs confirmed about a one week earlier onset of action, but no overall advantage in efficacy after six to eight weeks of treatment (80). Mirtazapine is also sometimes used as an adjunct to SSRIs and SNRIs; in the STAR*D study clinicians were better able to implement this combined therapy than make the switch to the MAOI tranylcypromine (81).

Treatment of Psychotic Episodes of MDD

Approximately 5% to 10% of depressed outpatients experience delusions or hallucinations; these episodes of MDD are subclassified as "severe, with psychotic features" in Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition - Text Revision (DSM-IV-TR). As patients with psychotic features generally do not respond to treatment with antidepressants alone, practice guidelines recommend treatment with the combination of an antidepressant and an antipsychotic medication (29). In current practice, most clinicians opt for medication combinations that include an SSRI or SNRI and one of the second-generation antipsychotic drugs (i.e., aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone). Although it is plausible that treatment with an atypical antipsychotic alone might suffice for at least some patients, this particular monotherapy strategy has not been extensively studied, and the RCTs that contrasted olanzapine monotherapy versus the combination of olanzapine and fluoxetine in psychotic depression yielded mixed results (82).

Augmentation Strategies

In addition to the use of antidepressants such as bupropion and mirtazapine in combination with the SSRIs and SNRIs, other medications that are not indicated as monotherapies for depression are often added to ongoing antidepressant therapy in an attempt to augment or enhance the outcomes of patients with nonpsychotic forms of MDD. Best studied among the older adjunctive strategies are lithium salts and thyroid hormone, with lithium having the stronger evidence base (83). However, most of the studies of lithium augmentation were conducted more than a decade ago and evaluated augmentation of TCAs, not SSRIs or SNRIs. The most recent larger-scale study of lithium augmentation, which was conducted as part of the STAR*D program, did not yield particularly positive results (84). With respect to adjunctive therapy with atypical antipsychotics, there is a progressively growing evidence base to suggest efficacy across the entire class (85), though only aripiprazole has received FDA approval for this specific indication on the basis of two well-controlled RCTs (86,87). At the time that this chapter was written, FDA applications for two other atypical antipsychotics (quetiapine and olanzapine in combination with fluoxetine) were under review. The major question pertaining to use of atypical antipsychotics as augmentation strategies is not whether or not they work, but rather what to do when they do work. In particular, the atypical antipsychotics are costly medications, and even with aripiprazole, which tends to have a more favorable metabolic profile (88), there are legitimate concerns about the risks of weight gain and other metabolic complications with longer-term use. Should patients who respond to adjunctive therapy with an atypical antipsychotic medication require therapy indefinitely, the uncertain ultimate risk of tardive dyskinesia must be taken into account.

Antidepressants and Suicide

The concern about an association between antidepressants and suicidal ideations and behavior is not new (89). Nevertheless, it gained widespread attention in 2003 and 2004 as part of a broader concern about the increasing use of antidepressants in children and adolescents (90–93). A review of the data from 24 double-blind, placebo-controlled RCTs of antidepressant therapy in youth led the FDA to conclude that there was about a twofold increase in risk of suicidal behavior during acute phase therapy (i.e., 4 per 100 on active drug as compared with 2 per 100 on placebo). Subsequently, the FDA reviewed larger data sets from RCTs of adults and concluded that there was a similar trend in adults of age 18 to 25. These findings suggest that treatment-emergent suicidal ideation is an age-dependent phenomenon, which could relate to either developmental factors (i.e., delayed maturation of inhibitory serotoninergic systems in some more vulnerable youths) or perhaps induction of mixed states in youths who will subsequently be recognized to have bipolar disorder. One important consequence of the FDA reviews is that all antidepressants now carry a "black box warning" about the risk of treatment-emergent suicidality. This publicity about this regulatory warning appears to have resulted in decreased prescription of antidepressants to youth (94,95), which in turn may have ended a 20-year decline in the rate of suicide in children and teenagers over the past two decades (96). Obviously, decisions about whether or not to prescribe an antidepressant as part of the treatment plan for a depressed teenager or young adult must take into account the risks of the illness, the potential risks of the treatment, as well as the knowledge that alternate interventions, such as psychotherapy, are available. Moreover, when the risks of prescribing are viewed to be acceptable and an antidepressant is prescribed, the treatment plan should include close follow-up and instructions about after-hours or emergency services.

Summary

A range of antidepressant medications are available to treat patients with MDD. As noted earlier, the SSRIs have emerged as the usual treatment of first choice for MDD because of a combination of qualities, including ease of use, tolerability, and safety. As there are now multiple generic formulations of all but one of the SSRIs, low acquisition costs provide a strong additional justification. Indeed, most pharmacy benefit plans now require at least one initial trial of a generic SSRI before moving on to other antidepressant options. It is also true that some people with MDD may preferentially respond to one agent over another at any given point in time. Unfortunately, no accurate method currently is available to permit practitioners to identify in advance the particular individuals who are unlikely to respond to an SSRI.

ACUTE PHASE PSYCHOTHERAPY

The so-called depression-focused psychotherapies have dominated this region of the therapeutic landscape since the early 1980s. A number of developments shaped a movement away from the psychodynamic psychotherapies that had dominated the field for the preceding decades (see Ref. 97 for a more detailed discussion). For example, the expected duration of psychodynamic psychotherapy was much greater than that of antidepressant pharmacotherapy, and time to expected symptom relief was viewed by some as unacceptably long. As

more and more individuals sought ambulatory mental health services, it was also evident that a larger number of nondoctoral-level counselors and therapists would be needed to meet the demand for services. As few of these mental health clinicians had psychoanalytic training, there were further pressures to develop more focused, "here and now" interventions that could be implemented in community settings. The development of manuals to specify the essential methods and guide learning also enhanced the reproducibility of the newer psychotherapies and permitted—for the first time—independent assessment of the fidelity and adherence to treatment protocols. The newer focused therapies also came on to the scene at a time in which there began to be a greater interest in documenting treatment efficacy (i.e., evidence that an intervention is effectively derived from controlled studies). The family of approaches known as behavior therapy (BT) grew directly from academic clinical psychology and was built on research using classical and operant conditioning models to change or modify overt behavior. Beck's model, cognitive therapy (98), also drew on behavioral formulations of depression, but placed a greater emphasis on the role of covert cognitive processes, including thoughts, attitudes, and beliefs, in both the genesis and persistence of depressive states. In addition, a growing appreciation for social and relational contexts of depression culminated in the model of interpersonal psychotherapy developed by Klerman and Weissman and their colleagues (99).

Another major advantage of the newer, focused psychotherapies was the willingness of the developers to conduct controlled clinical trials of treatment efficacy. The arrival of focused psychotherapies for treatment of MDD has led to a significant increase in research on psychosocial interventions for depression, including studies of relative efficacy in comparison with pharmacological control conditions. By contrast, many of the leaders of psychoanalysis and psychodynamic psychotherapy did not place a high value on this type of research. The apparent unwillingness of psychodynamically oriented academicians to conduct such studies ultimately inadvertently undermined their powerbase within academic medicine, where a premium is placed on level of research funding and number of high-impact publications in first-line journals. We will now proceed with a discussion of the current evidence base for acute phase psychotherapy for depression.

Cognitive Therapy

Cognitive Therapy (CT) is the best-studied psychological treatment of major depression and has been compared with waiting-list control conditions, other forms of psychotherapy, and antidepressant medications, both within designs using treatment-as-usual and standardized protocols for drug administration (100,101). In one meta-analysis of early studies, CT demonstrated an overall efficacy rate of 46.6% and a 30% advantage when compared with waiting-list controls (102). A smaller number of RCTs have studied CT in three or four arm designs that included a double-blind pill placebo. Not all of the placebo-controlled studies have confirmed efficacy (103,104), while others have (105,106). When considering such a mix of positive and failed studies, it is important to keep in mind that approximately one-half of RCTs of antidepressants fail to document significant drug versus placebo differences (21).

Although the methods of CT are particularly well suited to group therapy, only a small number of small RCTs comparing group and individual therapies have been conducted. In the Depression Guideline Panel (102) meta-analysis, group CT was found to be somewhat less effective than individual therapy

(50.1% vs. 39.2%). CT also has been adapted for treatment of hospitalized depressed patients (107–110). In the report of Thase and colleagues, more than 70% of a consecutive case series of 30 unmedicated inpatients with features of endogenous depression responded after up to four weeks of intensive CT. In two small RCTs of combined treatment (107,109), some evidence favored the combination of CT and antidepressants when compared with antidepressants alone, although in the study of Miller et al. (109) the additive benefit was largely limited to a subgroup of patients with high levels of dysfunctional attitudes.

With respect to comparative efficacy, results from studies comparing CT and TCAs generally report comparable efficacy across 12 to 16 weeks of acute phase therapy (see Refs. 97 and 102 for detailed reviews). Notable exceptions include an initial study by Beck's group, in which the results favored CT over imipramine (111); a study of HIV-seropositive men with relative milder depressions, in which imipramine was more effective than CT (112); and the multicenter, NIMH-sponsored Treatment of Depression Collaborative Research Program (TDCRP) study, in which imipramine was more effective in the subset of patients with more severe depressive symptoms (103,113).

The results of four more recent studies employing pharmacotherapy comparison groups are noteworthy, particularly because these studies compared CT with newer-generation antidepressant medications. In one that focused on low-income and minority women with MDD, Miranda et al. (114) compared a brief course of cognitive behavioral therapy (CBT) with a two-stage pharmacotherapy protocol. A third arm—referral to appropriate community agencies—served as a treatment-as-usual control condition. Results after six months indicated that depressed women who were randomly assigned to medication or CBT demonstrated significantly greater improvement in depressive symptoms than those referred to treatment as usual. While both active treatments were effective, one measure of treatment implementation strongly favored pharmacotherapy: 76% of individuals assigned to medication received nine or more weeks of therapy at acceptable doses, while only 36% of those assigned to CBT attended six or more sessions of therapy. This difference in treatment adherence likely accounts for the trend that favored pharmacotherapy in terms of final intent-to-treat remission rates, which were 44%, 32%, and 28% for the pharmacotherapy, CBT, and treatment-as-usual groups, respectively.

In the second RCT, which was conducted at the University of Pennsylvania and Vanderbilt (106), the efficacy of CBT was compared with a two-stage pharmacotherapy protocol in outpatients with moderate to severe MDD. In this study, patients were randomly assigned to initially receive CBT, paroxetine, or placebo. After 8 weeks, the placebo arm was closed (patients received alternate treatments) and those not responding to active paroxetine could receive augmentation with either lithium carbonate or desipramine (doctor's choice) for the next 8 weeks of the 16-week study. Both active interventions were significantly more effective than PBO at week 8, with response rates of 50%, 43%, and 25% for the groups randomized to medication, CBT, and placebo (PBO), respectively. At the end of 16 weeks, 58% of patients in each condition had responded to treatment, with remission rates of 46% for the medication group and 40% for the CBT group. Pharmacotherapy tended to be more effective than CBT at one study site, while CBT was more effective than pharmacotherapy at the other site.

A third large multicenter RCT examined the efficacy of a related form of therapy, cognitive-behavioral analysis system of psychotherapy (CBASP), which

was developed for treatment of patients with chronic depressive disorders (115). In this trial, CBASP was compared with the antidepressant nefazodone, both singly and in combination. CBASP differs from CT in several important ways, including the use of situational analysis of interpersonal interchanges to help chronically depressed patients learn specific goal-directed approaches to improving relationships. Keller et al. (115) found that the two monotherapies were comparably effective at week 12, although the group that received nefazodone therapy experienced more rapid symptom relief. The combination of CBASP and nefazodone was significantly more effective than either of the monotherapies, with intent-to-treat response rates at week 12 of 48% for CT alone, 48% for nefazodone alone, and 73% for the combination. Secondary analyses of the rates of change in symptom measures suggested that the advantage of the combined condition was achieved by merging the early symptom effects of nefazodone with the later emerging symptom effects of the psychotherapy; the advantage of combined treatment compared with CBASP alone was particularly evident among the patients with significant insomnia (116) and—as compared with nefazodone alone—among those with histories of early child abuse or parental neglect (117).

The fourth study, which was conducted as part of the STAR*D program, evaluated the utility of CT in patients who did not obtain adequate benefit from an initial course of therapy with citalopram (65,66). One unexpected finding of this study was that only about 30% of the eligible patients opted for randomization strata that included CT as an option. In this regard, CT was a less acceptable second-choice option than pharmacotherapy: approximately 55% accepted options that included switching antidepressants, and 45% accepted options that included pharmacological augmentation. Among those who agreed to participate, results were reported separately for individuals who accepted randomization to either augmentation of citalopram with CBT (n = 65) or medication (n = 117) and those who opted for a switch to CBT (n = 36) or another antidepressant (n = 86). Overall, patients who received CBT as a second-stage treatment (either alone or in combination with citalopram) had similar levels of improvement, response, and remission rates to those who received the various medication strategies. For those who continued to take citalopram, the addition of CBT resulted in significantly slower time to remission than did augmentation with medication (buspirone or bupropion). No significant outcome difference was noted among those who switched treatments, although tolerability indices favored the CBT group over the group that switched from citalopram to sertraline, bupropion SR, or venlafaxine ER. Thus, while CBT was a less acceptable second-step treatment than the alternate pharmacotherapies, at least within the design of the STAR*D trial, it was generally as effective—both alone and as an adjunct to continued citalopram therapy—as the medication approaches that were studied.

When taken together, these studies support the utility of CT for treatment of patients with MDD and, with only a few exceptions, suggest comparability with pharmacotherapy as first- or second-line interventions.

Interpersonal Psychotherapy

The efficacy of IPT has been studied in a number of RCTs of acute phase therapy of outpatients with nonpsychotic MDD. In an initial study, IPT was found to be

superior to a triage-based supportive treatment and comparable to treatment with therapeutic amitriptyline monotherapy during a 12-week clinical trial (118). Some evidence from this trial suggested that IPT was more effective than amitriptyline in terms of improvement in mood, suicidal ideation, and interest, whereas the pharmacotherapy intervention was superior in resolution of appetite and improvement in sleep disturbances (119). Combined treatment had additive benefit compared with either IPT or amitriptyline alone (118,119). The overall equivalence of IPT and pharmacotherapy has been further demonstrated by several other studies. In the NIMH TDCRP study, for example, IPT faired somewhat better than CT in that it was significantly more effective than placebo in the subanalyses of patients with more severe depressive symptoms and was not substantially less effective than imipramine (103,113). IPT was also significantly more effective than placebo and as effective as imipramine in the study of HIV-seropositive depressed men conducted by Markowitz and associates (112). In a study of patients treated in four urban primary care clinics, Schulberg et al. (120) tested IPT against both therapeutic nortriptyline and an unstructured therapy treatment-as-usual condition. The results indicated that nortriptyline was more rapidly effective, but that IPT became equally effective by the end of the trial. Both interventions were significantly more effective than the treatment-as-usual control condition.

Two other trials have examined the combination of IPT and pharmacotherapy during the acute phase of therapy (121,122). In the first trial, in which 193 outpatients with mild to moderate MDD were randomized for up to 16 weeks to receive IPT alone, nefazodone alone, IPT plus placebo, or IPT plus nefazodone, no significant treatment differences were found on the primary dependent measure, the HAM-D. On the MADRS, the combination of medication with psychotherapy was more effective in reducing depressive symptoms compared with medication alone, although the differences between the combination and either IPT alone or IPT plus placebo were not statistically significant. It should be noted that the lack of a PBO control group in this study limits interpretation of the findings, as it is possible that the outcomes of the nefazodone-alone condition would not have surpassed a placebo-only condition.

A second controlled trial of IPT tested the benefit of an intensive, hospital-based therapy program in 124 inpatients with MDD (122). A total of 124 depressed inpatients were randomized to receive either five weeks of treatment as usual (antidepressant pharmacotherapy and milieu therapy) alone or enhanced by 15 individual and 8 group IPT sessions. For patients treated with adjunctive IPT, intent-to-treat analyses revealed that adjunctive treatment provided a significantly greater reduction of depressive symptoms at week 5 as compared with the treatment-as-usual group. Response rates were 70% for the group that received adjunctive IPT, compared with 51% for the treatment-as-usual comparison group. Although not statistically significant, a smaller trend in remission rates was also evident (49% vs. 34%). A secondary analysis indicated that the advantage provided by adjunctive IPT was largely accounted for by superior outcomes in the subset of patients with chronic depressive syndromes (123).

In addition to these RCTs, further evidence of the potential utility of combining IPT and pharmacotherapy was found in the meta-analysis of individual patient data conducted by Thase et al. (124). This report compared the outcomes of nearly 600 patients treated with the combination of imipramine or nortriptyline and IPT versus those of patients treated with either IPT or CBT

alone. Results indicated a modest advantage for combined treatment overall, with a significant interaction between pretreatment severity and treatment outcome. Specifically, the advantage of combined treatment over psychotherapy alone was relatively small (~10% difference in remission rates) among the patients with milder depressions, but large (~30%) among the subset of patients with more severe, recurrent depressions.

As both IPT and CBT have been shown to be effective acute phase therapies, direct comparisons of these interventions are of particular interest. In addition to the NIMH TDCRP, three other RCTs have compared IPT with CT (112,125,126). In the first, as reviewed previously, Markowitz et al. (112) randomly assigned 110 HIV-seropositive men with depressive disorders to one of four treatment conditions: IPT ($n = 24$), CBT ($n = 27$), or supportive psychotherapy with ($n = 26$) or without ($n = 24$) imipramine monotherapy. At the end of the 17-week protocol, IPT and supportive therapy with active imipramine were equally effective. On most analyses, IPT was also more effective than CBT. The authors speculated that IPT may be a better fit than CBT for the real-world concerns of depressed HIV-seropositive patients.

The second trial, which was conducted in New Zealand, included a protocol that consisted of 16 weeks of individual therapy (125). While there were no overall significant differences between the two therapies in terms of symptom reduction or response/remission rates, results among the subset of individuals who scored 30 or higher on the pretreatment MADRS favored CBT over IPT. A secondary analysis also indicated that patients with personality disorders were less responsive to IPT, while Axis II pathology did not adversely affect response to CBT (127).

In the third recent trial comparing IPT and CBT (126), 56 Canadian outpatients with MDD were randomly assigned to undergo 16 to 20 sessions of individual therapy over a period of up to six months of acute phase therapy. While the two therapies were comparably effective overall, IPT demonstrated an advantage for patients with more secure attachment styles. CBT, on the other hand, offered significantly greater reduction in depression severity and greater likelihood of symptom remission in individuals who scored higher on attachment avoidance.

Although IPT may be viewed as an effective acute phase therapy, results of several studies suggest that IPT alone may be less useful for particular groups of depressed patients. The first potential indicator of poorer response to IPT is high levels of anxiety, which was identified in three different trials conducted by the Pittsburgh group (128–130). The second, and perhaps conceptually related indicator, is complicated bereavement. For example, in a small study of older patients with "bereavement-related depression," Reynolds et al. (131) found that IPT plus pill placebo was significantly less effective than therapy with the TCA nortriptyline alone, with the group receiving IPT showing no better response than the group that received a pill placebo alone. The combination of IPT and nortriptyline also did not enhance outcomes compared with pharmacotherapy alone in this study, though the group receiving combined therapy did have a lower dropout rate. In a second RCT of individuals who met criteria for depression and complicated grief (132), IPT was compared with a novel, more behavioral form of psychotherapy developed to more specifically address complicated grief. While participants in both therapies experienced a decrease in grief symptoms, those who received IPT were significantly less

likely to respond than those who received the novel therapy. Thus, although unresolved grief is one of the core theme areas targeted by IPT, it appears that individuals with more extreme or persistent bereavement symptoms may obtain greater benefit from either pharmacotherapy or a more behaviorally oriented intervention.

The third potential indicator of poor response to IPT alone is subsyndromal minor depression or dysthymia. In one of the largest studies of psychotherapy of depression ever undertaken, Browne and colleagues (133) evaluated the outcomes of 707 primary care adult outpatients with chronic dysthymic disorder, with or without a history of MDD. Patients were randomly assigned to IPT alone, sertraline alone, or the two strategies in combination. Results indicated that the patients who received sertraline had significantly better outcomes, with response rates among the completers at month 6 of 47% (IPT alone), 60% (sertraline alone), and 58% (combination). Similar results were found in the study of Markowitz et al. (134), which was conducted in 94 outpatients with dysthymic disorder. In this trial IPT and sertraline were again compared, both alone and in combination with pharmacotherapy, with a fourth arm, brief supportive psychotherapy (BSP), also included to control for the potential nonspecific effects of therapeutic support. They found that patients who received sertraline—whether alone or in combination with IPT—improved significantly more than those who received IPT or BSP alone. Response rates were 58% for sertraline alone, 57% for combined treatment, 35% for IPT, and 31% for BSP.

A fourth potential indicator, medical complexity, is suggested by the results of the cardiac randomized evaluation of antidepressant and psychotherapy efficacy (CREATE) study (135). This 12-week RCT enrolled 284 patients from nine academic centers, and used a 2×2 factorial design to randomly assign patients to receive 12 weekly sessions of IPT plus clinical management ($n = 142$) or clinical management only ($n = 142$), in combination with either citalopram ($n = 142$) or pill PBO ($n = 142$). Whereas citalopram was found to be superior to PBO in terms of symptom reduction and remission rates, IPT was no more effective than clinical management, whether it was combined with citalopram or PBO.

There is now strong evidence that IPT is an effective acute phase treatment for outpatients with MDD, both alone and in combination with antidepressant medications. The additive value of these strategies appears to be greatest for patients with more severe depressive episodes. IPT and CBT probably have comparable benefit overall, although IPT may be somewhat less useful for patients with dysthymia and those with complicated bereavement, significant anxiety, or medical complexity.

Behavior Therapy

The term behavior therapy (BT) is used to describe a family of interventions that include problem solving, social skills training, and behavioral activation. Collectively, BT is one of the oldest forms of focused psychotherapy, and efficacy has been established versus both waiting-list control groups and antidepressants (102,136,137). When studies of the many variants of BT are considered together, the weight of the evidence is sufficient to conclude that these strategies are useful acute phase therapies. In the Agency for Health Care Policy and Research

(AHCPR) meta-analysis of early studies, for example, an overall intention-to-treat efficacy rate of 55.3% was observed for BT on the basis of data from 10 suitable studies. Like CT, BT is well suited for group applications.

Several studies that have ensured comparable therapeutic expertise have directly compared BT with CT; results overall suggest that relatively simpler models of BT can produce gains that are comparable to those resulting from the more elaborate CT. For example, Jacobson and colleagues (138) conducted a study in 151 MDD outpatients comparing 16 weeks of treatment with behavioral activation against both the full model of CT and an attenuated intervention that focused on automatic negative thoughts. They found no meaningful differences across the three treatments, with response rates ranging from 58% to 68%. Pretreatment symptom severity did not predict differential response. A subsequent study by this group compared 16 weeks of behavioral activation with CT and the SSRI paroxetine (104). During the first eight weeks of the study, a double-blind pill PBO group also was included. The study group was stratified by level of depressive severity at study intake, with participants scoring 19 and lower classified as "low severity" and those scoring 20 and higher classified as "high severity." As in the NIMH TDCRP study, there did not appear significant differentiation among the therapies in the patients with lower symptom levels. By contrast, the efficacy of paroxetine was confirmed versus placebo at week 8 in the patients with more severe depression and—at week 16—both behavioral activation and paroxetine were significantly more effective than CT on measures of depressive symptoms. Results of a secondary analysis suggested that the relatively poor performance of CT in this study was accounted for by a subset of patients characterized by more severe, chronic depressions, with higher levels of functional impairment and more long-standing interpersonal problems (139).

Psychodynamic Psychotherapy

After several decades of little activity (with respect to conducting comparative clinical trials), psychodynamically oriented researchers have begun to conduct RCTs of time-limited models of psychotherapy. In the first wave of studies, psychodynamic psychotherapies were often compared with cognitive-behavioral interventions. The first such study, the Sheffield Psychotherapy Project, randomized 40 patients who met criteria for a depressive or anxiety disorder to eight weeks of therapy with either a psychodynamic, exploratory intervention or a standardized cognitive-behavioral intervention (140). After completion of the first eight weeks of treatment, patients were crossed over to the alternate intervention; the same therapists provided both forms of therapy. Results tended to favor the cognitive-behavioral treatment, although the differences were modest. The findings of the second Sheffield psychotherapy project, in which 117 depressed outpatients were randomized to either 8 or 16 weeks of psychodynamic psychotherapy or cognitive-behavioral therapy, generally mirrored those of the first, with the longer treatment course producing better outcomes among the subset of patients with more severe depressive symptoms. A third study, the Helsinki psychotherapy study ($n = 381$), compared a brief behavioral intervention, solution-focused therapy (SFT), with shorter and longer-term psychodynamic psychotherapy in patients with depressive and anxiety disorders (141). No significant differences among the treatment groups were

observed on a wide range of depression and anxiety measures. A fourth RCT, which focused on treatment of 193 women with postpartum depression, compared nondirective counseling, cognitive-behavioral therapy, and psychodynamic therapy with a control condition of routine primary care (142). All three treatments demonstrated significant impact at 4.5 months, but only psychodynamic therapy produced a reduction in depression that was statistically significant to the control condition.

A series of studies conducted in the Netherlands examined a manual-based model of brief dynamic psychotherapy (BDP) in outpatients with MDD (143–146). In the first trial (143), 167 outpatients with mild to moderate forms of MDD were randomized to receive six months of treatment with either 16 sessions of BDP plus antidepressant medications or antidepressants alone. The antidepressant protocol was flexible, and permitted three steps across six months of randomized treatment: fluoxetine, followed by amitriptyline and the MAOI moclobemide, if necessary. In terms of both acceptability of treatment and outcome, the investigators found significant differences that favored combined treatment over pharmacotherapy alone. Response rates after six months of study treatment were 59% for patients who received combined therapy and 41% for patients who received only pharmacotherapy. A second report (147) from this trial reported that the advantage of combined treatment was largely explained by the outcomes of patients with comorbid personality disorders, who tended to respond poorly to pharmacotherapy alone; the added benefit of combined treatment was small among the subset of patients who did not have personality problems.

The second study by this research group investigated whether combined therapy demonstrated advantages over SDP alone (144). Using a similar six-month protocol, 191 patients with mild to moderate MDD were randomized to receive either BDP alone or BDP in combination with antidepressant pharmacotherapy. The pharmacotherapy protocol in the study was updated to include four steps: the SNRI venlafaxine, SSRI, nortriptyline, and nortriptyline plus lithium. Fewer significant differences were evident in this study, though the combined therapy group was found to have more improvement on the patient self-report measure of depressive symptoms.

Results of these trials were pooled with those of a third smaller study (145) to conduct a meta-analysis of individual patient data comparing the three strategies (dynamic psychotherapy alone, pharmacotherapy alone, and combined treatment) (148). In the pooled data set, combined therapy was found to be superior to pharmacotherapy alone in terms of ratings by patients, therapists, and independent evaluators. Combined treatment was superior to psychodynamic psychotherapy alone on only the patient-reported outcome measure; there was a strong trend on the independent observer-rated HAM-D, but little difference on the therapist-rated variable. A fourth study by this group (146) focused on the speed of response to treatment with BDP versus pharmacotherapy. A total of 141 outpatients with MDD were randomized to the two modalities, with results favoring pharmacotherapy at the week-4 assessment but showing no difference at week 8.

Although the evidence base for psychodynamic psychotherapy is less robust than it is for CT and IPT in studies of MDD, the database is growing and, overall, the findings suggest that BDP is effective, both alone and in combination with antidepressants.

TREATMENT OF MDD IN THE LONG TERM

Depression frequently runs an episodic or recurrent course, and in current practice longer-term models of pharmacological treatment are often recommended to attenuate these risks. By convention, the acute phase of therapy ends when a patient obtains a good response or (ideally) remission, at which point the second or continuation phase of therapy begins (28,29). In fact, it is now the standard of practice for essentially all patients who respond to antidepressants to receive at least six months of continuation phase therapy (29,36). The goals of continuation phase pharmacotherapy are not only to reduce the risk of relapse but also to help ensure that the patient obtains a stable remission with eventual restoration of functional capacity (29). As the continuation phase progresses, patients are seen less frequently, with the norm typically being monthly sessions during the final months of the continuation phase.

There is strong empirical support for this recommendation. For example, a meta-analysis of placebo-controlled RCTs of continuation phase pharmacotherapy found that patients who were switched from active antidepressants to placebo following acute phase therapy had essentially twice the risk of relapse across a six- to nine-month interval (149). It appears that all antidepressant medications are effective for prevention of relapse, although there are differences among drugs in terms of risks of persistent side effects, such as sexual dysfunction, and later emerging side effects, such as weight gain (36).

One of the strongest predictors of relapse during continuation phase pharmacotherapy is incomplete remission (16,150). In a study designed to test the impact of a course of adjunctive, time-limited psychotherapy on this risk, Paykel et al. (151) randomized 158 incompletely remitted patients to either pharmacotherapy alone or in combination with 16 sessions of CT. They found that the adjunctive therapy was effective, reducing the risk of relapse by about 20% across 18 months. A subsequent report by Paykel et al. (152) evaluated patient outcomes for 4.5 years after completion of the first study (i.e., 6 years after randomization). They found a significant preventive effect for CT for more than three years after termination of therapy.

For patients who respond to psychotherapy alone, there is no consensus about when therapy should be extended beyond 12 or 16 weeks. In some ways, thinking about longer-term models of time-limited psychotherapy borders on the heretical, as the briefer nature of these interventions has been one of their most important differentiating characteristics (97) and, indeed, the effects of CT have been shown to be more durable following termination of therapy than are the effects of antidepressants following withdrawal of pharmacotherapy (see the meta-analysis of Vittengl et al. in Ref. 153). Nevertheless, the risk of relapse after time-limited therapy of depression is not trivial, and as there is some evidence that patients who continue to manifest a significant level of residual symptoms are at increased risk for relapse following time-limited psychotherapy (17), more extended models of targeted therapy have been developed. In the study of Jarrett and colleagues (154), a structured course of 10 sessions of CT conducted across the first eight months after completion of acute phase CT significantly reduced the risk of relapse, particularly among the subset of patients who were incompletely remitted at the end of the acute phase of therapy.

Whereas there have been only a handful of studies of maintenance phase psychotherapy, there have been a large number of placebo-controlled studies evaluating maintenance phase pharmacotherapy across 12, 18, or 24 months

(155). Indeed, maintenance phase therapy is typically recommended following the continuation phase for antidepressant responders judged to be at high risk for recurrent depression (i.e., those who have experienced three or more prior episodes, with three lifetime episodes or two episodes within the previous five years considered to identify those at greater risk) (29,155). During the maintenance phase, some patients will continue to be seen monthly, though more often than not the frequency of visits diminishes over time to quarterly, semi-annually, or eventually an annual basis. As in continuation phase therapy, the dose of medication is typically held constant during maintenance phase therapy, unless side effects become problematic (29,155). Although dose reduction may help to lessen side effects, it should be done with some trepidation, because reducing doses also decreases the preventive efficacy of pharmacotherapy (156–159).

Some speak of maintenance phase pharmacotherapy as a life-long requirement, whereas others take a more indefinite approach (155). From either perspective, maintenance phase pharmacotherapy usually does not have a finite endpoint, and for patients who have clearly responded to an antidepressant and who have a history of suffering recurrent episodes in the past when tapered off antidepressants, maintenance phase pharmacotherapy is the best-proven strategy to minimize the likelihood of subsequent recurrent depressive episodes. In this regard, the risk of recurrence following withdrawal of antidepressant medication is substantial even after one (160) or three (161) years of successful maintenance phase therapy. The expected benefits of continuing pharmacotherapy, as well as the known risks and costs of continuing to take the antidepressant, should be reviewed periodically during semi-annual or annual medication monitoring visits (155).

For patients who have been treated with the combination of psychotherapy and pharmacotherapy during the acute phase, it would be worthwhile to know if both forms of therapy are beneficial during the maintenance phase. In a series of seminal studies conducted at the University of Pittsburgh, the value of combined maintenance phase treatment with IPT and antidepressant medication was demonstrated (in comparison with pharmacotherapy alone) in one study of depressed patients of age 60 and older (162) but not in studies of adults of age 18 to 65 (163) or adults of age 70 and older (164). In all three studies, psychotherapy alone was not an effective alternative to ongoing pharmacotherapy (either alone or in combination with IPT).

Two studies have evaluated models of maintenance phase psychotherapy for patients at high risk for recurrence who responded to psychotherapy alone during the acute phase of treatment. In the first trial (165), 82 patients with chronic forms of MDD who had responded to a 12-week course of CBASP during acute phase therapy and who had not relapsed during a 16-week course of continuation phase therapy received one year of additional follow-up, with random assignment to either monthly sessions of therapy or an assessment-only control condition. Patients who were allocated to the CBASP condition were significantly less likely to suffer a recurrent depressive episode and had significantly lower levels of depressive symptoms than those in the assessment-only condition. In the second study, Frank et al. (166) evaluated three doses of maintenance phase IPT (weekly, biweekly, and monthly) for prevention of recurrent MDD across a two-year interval. A total of 233 women with a history of recurrent depression were initially treated with IPT, of which 99 remitted on IPT alone and 90 remitted only after an SSRI was added to the treatment

regimen. They found that although the dose of maintenance IPT was not related to recurrence risk, only 36% of patients who remitted with IPT alone suffered a recurrent depressive episode. By contrast, only 36% of the group that required an SSRI was able to remain well with IPT alone, following drug discontinuation, and one-half of these patients suffered a recurrent depressive episode during the two-year course of IPT maintenance therapy.

Another interesting application of focused psychotherapy involves sequential treatment of antidepressant responders during the continuation or maintenance phase, with the ultimate goal reducing the risk of recurrence following withdrawal of medication. Several groups have tested various models of cognitive-behavioral therapy. In the first such study, Fava and colleagues (167) tested the impact of a variant of CT known as personal well-being therapy in 40 patients with recurrent MDD; all patients were on stable doses of maintenance antidepressant therapy at the outset of the study. During the 20-week experimental phase, all patients were withdrawn from antidepressant medications; subsequently the study group was followed for two years. They found that this relatively short course of individual sessions resulted in a significant reduction in recurrence risk (80% vs. 25%), with a significant decrease in residual symptoms and a much lower incidence of resumption of antidepressant therapy during the follow-up. In the second study, patients with recurrent MDD were randomized to receive either treatment as usual alone or in combination with a time-limited course of group CT. Outcomes were assessed by blinded evaluators over two years. There was a significant effect for CT intervention, particularly among the subset of patients who had suffered a greater number of past episodes of depression.

Two other studies have evaluated mindfulness-based cognitive therapy (MBCT) for prevention of recurrent depression in patients who have been taking maintenance phase pharmacotherapy (168,169). This group intervention differs from conventional CT in that patients are taught to disengage from the automatic negative thoughts that are associated with low moods, rather than to attempt to use cognitive strategies to test and, if possible, rebut the negative thoughts. In the first study (168), 145 recently recovered yet unmedicated patients with a history of recurrent depression were randomly assigned to receive either treatment as usual alone or in combination with MBCT; participants were followed across 60 weeks. MBCT was associated with a significant reduction in the risk of relapse/recurrence for the patients with a history of three or more lifetime episodes of depression. No such effect was observed among the subset of patients who had only experienced two prior depressive episodes.

The utility of MBCT was confirmed by the results of a second study (169), in which 73 recovered patients with a history of recurrent MDD were randomized to receive either treatment as usual alone or in combination with MBCT. Among the subset with a history of at least three lifetime episodes of depression ($n = 55$), the difference in relapse rates strongly favored the group that received MBCT (36% vs. 78%). As in the first study, no advantage was found for MBCT among the 18 patients with a history of only two past depressive episodes.

SUMMARY

This sweeping chapter attempts to bring together several lines of evidence-based psychiatric practice. Initially we covered clinical approaches to acute and longer-term treatment of MDD from a clinical application point of view. We discussed

adequate individual patient trials of medication monotherapy, augmentation therapy, and combination therapy. These latter two items are covered in depth in subsequent chapters in this book. We briefly discussed antidepressant trial design to offer the reader more insight into how trials are designed and used statistically to develop the evidence base from which we choose our antidepressant prescriptions to treat our patients. Instead of listing hundreds of individual studies, we grouped antidepressants into clusters of medications, and brought the reader's attention to some standard medication outcomes both in the short term and the long term. It makes sense, when treating depression, that we understand the potential outcomes for our patients. We should be able to educate our patients on their prognosis and potential outcomes. Again, much of this chapter focuses on acute depressive episodes and does not take into account resistant depression. Later in the book, treatment-resistant depression is addressed clinically, by evidence-based trials, and also by evaluating the outcomes of the large NIH STAR*D trial. Obviously, treatment-resistant depression may have different outcomes than reported in the trials noted above. Finally, we addressed different types of psychotherapy, short term and long term, in regards to their individual evidence bases as well. It is our hope that this chapter draws together some of these items and will allow the psychiatric clinicians to improve their integrated scope of practice.

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3 Combining Medications to Achieve Remission

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INTRODUCTION

Depression is currently among the most treatable illnesses that we see in medicine. Similar to any other medical illness, depression should be treated to full remission and, ultimately, to recovery. Remission has now become the standard of care for treating individuals with major depression, and should be the goal of treatment for the patient who partially responds in the first episode or the patient who may have failed to respond to multiple treatments. Unfortunately, up to 50% of patients who "respond" to their antidepressant treatment fail to fully "remit" (1). Data from long-term clinical trials of antidepressant response have estimated that approximately two-thirds of patients fail to achieve full remission (2). More recent findings from the National Institute of Mental Health's Sequenced Treatment Alternatives to Relieve Depression (STAR*D) suggest that in a community sample of patients with depression, approximately 40% of patients failed to "respond" to an adequate trial of a selective serotonin reuptake inhibitor (SSRI) and over 65% failed to achieve remission (3). This study went on to show only modest improvement of response or remission and high rates of residual symptoms, even when patients were given a chance to switch antidepressants or augment their treatment to a set sequence of treatment choices (4,5). Furthermore, acute and long-term studies show that high rates of "residual symptoms" persist even after remission is achieved in the treatment of depression (1,6), and these residual emotional or physical symptoms of depression jeopardize achieving remission and can also significantly increase the risk of relapse and recurrence (7). In addition to increased risk of relapse and recurrence, there are several other possible consequences of failing to achieve remission, including continued psychosocial impairments, increased use of medical services, potential worsening of prognosis of any comorbid medical/psychiatric illnesses, ongoing risk of suicide, and at least the theoretical possibility of the patient becoming "treatment resistant" (8,9).

In the last several decades, an abundance of pharmacological, psychological, and other somatic treatment options for the effective treatment of depression have been introduced. There is also a growing literature on both the acute and long-term efficacy of these treatments used either alone or in combination with each other. These findings have been and will be extensively discussed in other chapters. One of the more common themes that has emerged in the last several years is the importance of treating the index episode of depression as aggressively as possible to achieve remission and continue to monitor to prevent relapse and recurrence. Remission remains among the strongest variables that predict whether a patient will do well in the long term (9).

The American College of Neuropsychopharmacology Task Force recommended that "full remission" be defined as an absence of both sad mood and reduced interest for at least three consecutive weeks in addition to the presence of three or fewer of the seven remaining *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, for symptoms of major depressive disorders (MDDs) (10). In clinical research, one of the accepted definitions of remission is a Hamilton depression rating scale (HAM-D)-17 score of 7 or less (11–13). This is in contrast to "response," which has been defined as having a minimum of a 50% decrease from baseline in the total HAM-D-17 score (11–13). It is not uncommon for patients to respond by having a drop in their baseline HAM-D-17 score of more than 50% but fail to achieve a remission HAM-D-17 score of 7 or less. In clinical practice, patients are said to be in remission when they are virtually asymptomatic and, over time, have a return of psychosocial functioning to that of their premorbid state (11–13). Remission remains a significant unmet target in the treatment of depression, and clinical expectations are moving toward defining more specific strategies to get depressed patients into full remission and subsequent recovery.

STRATEGIES TO ACHIEVE AND SUSTAIN REMISSION

MDD carries significant morbidity and mortality if not treated or if inadequately treated, the latter being defined as a condition in which a patient may be responding to treatment but continues to have residual depressive symptoms. A clinician must always consider the risk/benefit ratio of specific treatment strategies that should be tailored to an individual patient. Educating patients that the goal of treatment is complete symptom resolution is vital, in addition to confirming the diagnosis and comorbidities. It is also important to ensure adequate dosage and duration of each specific treatment. Inadequate dosing or duration of a "therapeutic dose" is a common error made in what may otherwise appear to be treatment failure. Maximizing the dose of a primary antidepressant should always be considered even for antidepressants that have not been shown to have a dose-response effect. Medications such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and venlafaxine [a serotonin-norepinephrine reuptake inhibitor (SNRI)] are examples of medications that may have a dose-response effect in some patients, and maximizing the dose of a particular antidepressant should be considered as long as it is not at the risk of tolerability and/or safety issues. Antidepressant dosages in some patients may be safely increased to the equivalent of 500 mg/day of imipramine (14–16). In the case of TCAs, monitoring the blood levels of the antidepressant or checking an electrocardiogram to ensure cardiac safety in such doses may be recommended. While some patients may respond to a treatment within the first 2 to 3 weeks of the antidepressant, others may not show a response for 12 to 16 weeks, and full response may not be evident until the latter time. Tolerability and safety issues are paramount in treating all depressed patients whether using monotherapy or combination treatments, and the clinician needs to remain cognizant of these issues over time because patients may develop comorbid medical illnesses or other factors that may affect the safety and tolerability of a particular treatment. Additionally, clinicians should always remain cognizant of problems with adherence to treatment because it is among the more common causes of failure to achieve and sustain a remission.

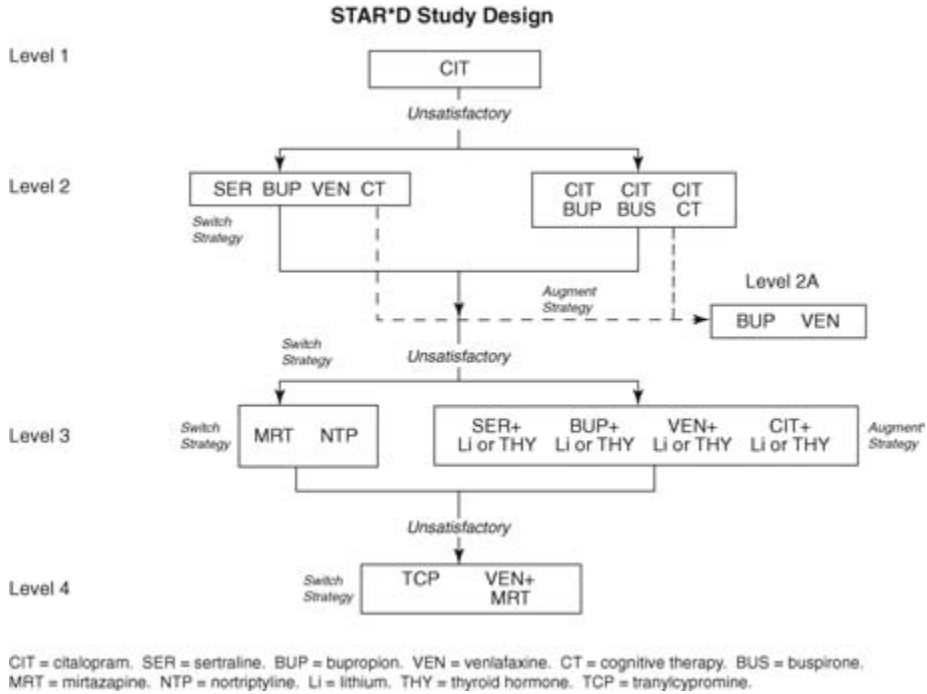

FIGURE 1 STAR*D study design. *Abbreviations*: CIT, citalopram; SER, sertraline; BUP, bupropion; VEN, venlafaxine; CT, cognitive therapy; BUS, buspirone; MRT, mirtazapine; NTP, nortriptyline; Li, lithium; THY, thyroid hormone; TCP, tranylcypromine. *Source*: From Ref. 17.

If monotherapy with a particular treatment is not effective, the clinician should then consider one of several strategies, including switching the antidepressant, combining antidepressants or augmenting the antidepressant with another somatic/pharmacological treatment. The sequence of switching, augmentation, or combination still requires "individualizing" the treatment to the individual patient and symptoms. The field is just beginning to recognize the importance of testing empirical evidence-based strategies to guide clinicians. However, these studies often have their own limitations, as the challenge to obtain data for evidence-based treatments are commonly associated with at least some methodological restrictions. The STAR*D trial (discussed in detail in a following chapter) provided clinicians and patients a selection of switch/augmentation/combination strategies (Fig. 1); however, these choices were limited by several factors, including the level of treatment the patient still failed to remit, maximal dose restrictions, and other variables that may have prevented higher remission rates (3). Therefore, evidence-based treatments should be considered as a guide to selecting a treatment strategy that is tailored to an individual patient. Additional considerations include psychotherapeutic interventions and other somatic treatments including electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS), phototherapy, and even "investigational treatments" (Table 1).

TABLE 1 Antidepressant Augmentation Options for Resistant Depression

L-Methylfolate
Lithium
Thyroid hormone
Buspirone
Stimulants
Amphetamine
Methylphenidate
Atypical antipsychotics
Benzodiazepines
β-Blockers
Pindolol
Propranolol
Modafinil
Steroid hormones
Estrogen
Testosterone
Anticonvulsants
Lamotrigine
Carbamazepine
Divalproex acid
Gabapentin
Other agents
SAMe
Atomoxetine
Buprenorphine
Ketamine
Riluzole
Tramadol
Dopamine agonists
Other somatic treatments
Electroconvulsive therapy
Vagus nerve stimulation
TMS
Phototherapy
Empirical psychotherapies
CBT
IPT
CBASP

Source: Adapted from Ref. 18.

TREATMENT-RESISTANT DEPRESSION

Despite the increasing literature on treatment-resistant depression, this population remains poorly defined. This chapter addresses the use of combination treatments in a "treatment-resistant patient"; however, this can describe a patient who is showing a partial response to the first antidepressant or a patient who has potentially failed to show any response to multiple antidepressant treatment strategies. The various clinical presentations of a treatment-resistant patient include: (*i*) the patient who shows a response or near remission yet has residual symptoms of depression; (*ii*) the patient who shows a response or remission and subsequently relapses or suffers a relapse or recurrence later in the course of treatment; or (*iii*) the patient who completely fails to respond to treatment. Before making a decision regarding the treatment for any of these

patient subtypes, clinicians should always attempt to identify any potentially "modifiable" factors that account for the lack of an acute or long-term remission. These factors include an accurate diagnosis, failure to achieve remission of the index episode, an inadequate trial of the treatment (dose and/or duration), problems with adherence, failure to keep the patient engaged in the treatment process, intolerance to treatment, inaccurate assessment of response, and psychosocial factors that prevent a full remission. Managing any of these modifiable factors should always be considered when facing a patient who appears to be resistant to treatment, whether it is the first treatment or a failure to respond to multiple treatment trials.

Managing these patients also includes confirming the presence or absence of all potential diagnoses, especially other axis I disorders that may be contributing to what may otherwise appear to be depressive symptoms or loss of an initial response. Examples include the discovery of a patient with bipolar disorder, psychosis, substance use disorder, anxiety disorder, or eating disorder. It is important to consider the role of axis II disorders in contributing to a lack of achieving an optimal antidepressant response, and clinicians should be encouraged to treat the axis I disorder aggressively. Axis II traits can improve when the underlying mood disorder is improved, particularly for patients with chronic or recurrent mood disorders. It is also important that clinicians have reasonable expectations about overt axis II pathology that may improve the outcome with adding a psychosocial management strategy. Additionally, considering the role of ongoing or new medical illnesses (axis III) that may complicate an underlying depression needs to be a part of the acute and long-term management strategies for any clinician who treats depression.

MAKING THE DECISION TO SWITCH, COMBINE, OR AUGMENT AN ANTIDEPRESSANT

When a patient is failing to respond optimally to a particular antidepressant treatment, the clinician is faced with making a decision to either switch to another antidepressant, combine the existing antidepressant with another (including "bridging" one antidepressant with another with the intention of stopping the first antidepressant), or augment the existing treatment. While there is a growing literature in regard to providing guidelines for clinical practice based on clinical research, it is important for the clinician to tailor his or her decision to an individual patient's needs. Before making a decision to switch, combine, or augment, it is imperative to ensure that the dose of the antidepressant has been maximized for an adequate duration of time, at least four to six weeks of an adequate dose, although other factors such as suicidality, psychotic symptoms, persistent anxiety, or severity of the underlying depression are examples of situations where combining or augmenting may need to occur at an earlier time. The quality of published reports on combining or augmenting antidepressants to achieve optimal responses has improved over the last several years; however, there are still significant methodological limitations with many of the studies. The assessment of baseline severity and comorbidity before the initiation of the primary antidepressant, the variety of patient subtypes including severity, chronicity, and history of treatment resistance of the depressive subtypes, and also whether the study is placebo controlled or based on open-label or case reports are factors that can impact what we extrapolate

from the clinical research literature. The clinician should remain aware of the current literature in regard to combining or augmenting antidepressants in specific patient populations and consider the methodology of published studies in terms of extrapolating the use of such strategies in their own clinical practice. It is helpful to refer to published literature when using specific strategies, especially when documenting this in the patient's chart as well as when obtaining informed consent from the patient. The clinician may feel more comfortable in utilizing a strategy that has been Food and Drug Administration (FDA) approved and well substantiated in the literature with double-blind, placebo-controlled trials that demonstrate both safety and efficacy compared with an open series of case reports that suggests efficacy and may be limited in describing safety and tolerability.

In addition to staying informed on the evidence in the literature in regards to safety and efficacy, other factors that the clinician should consider when deciding what to do when the initial antidepressant fails to provide remission include the cost of treatment, the potential for drug interactions, adherence, the rapidity of response, the type of symptoms that the patient continues to present with, family history, previous treatment history, and the degree of symptomology. When the clinician is faced with the choice of either augmenting or combining an antidepressant, there are some very basic guidelines that may help make the decision. Our group finds that, if a patient has less than 25% efficacy after an adequate dose and duration monotherapy, we may be more likely to consider switching the antidepressant rather than augmenting with a pharmacological agent that alone may not have inherent antidepressant effects. In this process, the clinician can consider combining two antidepressants as long as there are minimal issues with safety or tolerability. If the patient remits in the process of the switch during this "bridging" of antidepressants, the clinician may choose to continue the patient on the combination. For a patient who shows greater than 50% effect to a particular antidepressant, the clinician may augment the antidepressant with another pharmacological strategy to "enhance" the primary antidepressant effect, rather than risking switching to an antidepressant that may not provide the same degree of improvement as the initial treatment. Finally, for patients who fall between 25% and 50% improvement, switching versus augmenting the primary antidepressant needs to take into account the factors mentioned above, including questions such as: Is this the first treatment the patient failed? Has the patient failed multiple trials of several classes of antidepressants? How does the patient feel about the strategy?

There are a number of practical issues to consider when augmenting or combining antidepressants. It is important to tailor the choice of the treatment to the symptoms. It is also important to consider "synergistic" pharmacological profiles. For example, if the individual is on an SSRI, adding a noradrenergic or dopaminergic agent may be warranted (atomoxetine, stimulants, bupropion). For depressed patients who have comorbid illnesses that contribute to the underlying residual symptomology, using pharmacological strategies to target the symptoms may be warranted, examples of which include the following: for attention-deficit disorder, adding a stimulant or atomoxetine; for obsessive-compulsive symptoms, premenstrual dysphoric disorder symptoms, or eating disorders, the use of an SSRI may be warranted; for anxiety disorders, using buspirone, benzodiazepines, or even atypical antipsychotics may be considered; and, for bipolar disorders, the use of lithium, lamotrigine, carbamazepine,

divalproex sodium, or atypical antipsychotics may be considered. Moreover, side effects from the primary antidepressant may guide a clinician to choose a particular pharmacological strategy. For example, a patient who may be suffering sexual side effects and continues to have depressive symptoms may benefit from adding bupropion or a stimulant. Another example is a patient who may be showing a partial antidepressant response but has symptoms of "asthenia" or "tachyphylaxis" (apathy, fatigue, blunted affect, etc.) and for whom adding a stimulant, bupropion, atomoxetine, modafinil, or an atypical antipsychotic may be helpful. Finally, checking for psychotic symptoms that can often be subtle in many patients and the addition of an antipsychotic may bring the patient who fails to optimally respond to treatment to a complete response. All of these are examples of the art and the science of managing patients who are failing to remit on the current antidepressant. Data concerning these strategies is limited but will be covered later in this chapter.

If the clinician chooses to switch an antidepressant, consider whether the two antidepressants should be overlapped ("bridging") or the first antidepressant should be washed out before starting the second. The disadvantages of washing out may be the possibility of worsening of underlying symptoms, prolonging the depressive symptoms and/or the patient experiencing a possible antidepressant discontinuation syndrome. On the other hand, the advantages of washing out medications may be the prevention of potential drug interactions or additive side effects in some patients. Clearly, there are some antidepressants that are absolutely prohibited owing to tolerability issues and, more importantly, safety concerns. Examples of these include the use of MAOIs with other antidepressants without an adequate washout to avoid the potential for hypertensive reactions, a serotonin syndrome or cardiovascular effect (14–16). Overlapping treatments may help avoid the possibility of an antidepressant discontinuation syndrome when moving to the use of an antidepressant with a similar pharmacodynamical profile. Titrating down the first antidepressant while titrating up the second antidepressant is another alternative. Combining antidepressants during a switch may give the patient an opportunity to show an enhanced efficacy, particularly when using antidepressants with different pharmacological profiles. An example may be when moving from an SSRI to bupropion.

In summary, the clinician should not only take into consideration the issue of efficacy, but it is imperative that he or she be aware of drug interactions, safety, tolerability, cost, patient preference, and adherence issues. Sometimes a "win-win" scenario occurs when a clinician adds two medications to enhance efficacy and also has a resultant decrease in adverse effects as medications may treat each other's side effects as well.

DOCUMENTATION DURING THE MANAGEMENT OF COMBINATION STRATEGIES

It is important for clinicians to keep written records of past and current treatments (including the doses, duration of each dose, tolerability, and efficacy) available at all times. Our group finds it helpful for patients to use some form of life-charting techniques to ascertain the level of subjective and objective improvement that the patient experiences, as well as to serve as an additional tool to show patterns of response, adherence, and other potential factors that

may impact the outcome (e.g., menstrual cycle, substance use, and other factors). It is important to obtain verbal informed consent before all interventions, especially when using combination strategies that are not FDA approved, that is, "off label." This informed consent should describe the risk and benefit to the patient, explaining in detail the nonapproved status of these combinations and their side effects. It is important to let the patient ask questions and to involve significant others whenever possible. The patient should be kept updated with information, and it should be documented that the information was provided to the patient. When there is an absence of literature, clinicians may rely on theoretical ideas of clinical utility, which suggest that certain deficiencies in specific neurotransmitter systems or receptors may be the underlying cause of specific depressive symptoms. For example, an MDD patient who remains fatigued and unable to concentrate may preferentially benefit from the use of a drug that enhances noradrenergic activity. A clinician who treats MDDs with augmentation/combination treatment must become adept in this art and science of treating depression, stay informed about innovative treatment strategies, and be able to explain these options coherently to the patient whether on or off label.

Clinicians should feel comfortable when seeking second opinions or consultations either to confirm diagnoses or to confer with experts on the use of particular combinations or treatment strategies, including expertise in particular somatic, psychosocial, or investigational treatments. Tailoring the treatment to the needs of the individual over time is part of the art and science of treating any patient with major depression to achieve optimal recovery.

AUGMENTATION STRATEGIES

L-Methylfolate, Methyltetrafolate

It may be prudent to start this chapter with a full discussion about folate and methylfolate (MTHF) as one of the newest depression FDA approvals has been granted to MTHF (L-methylfolate, methyltetrafolate) as it now has an indication as an augmentation to antidepressant therapy. MTHF (Deplin®, PamLab, Louisiana, U.S.) recently received an indication as a "medical food" for "major depressive disorder that has not fully responded or may not fully respond to antidepressant therapy." MTHF is metabolite of folate (this active bioavailable form crosses the blood-brain barrier) that is available only by prescription. The current indication label for depression augmentation is for depression associated with low serum folate or red blood cell (RBC) folate. Limited data suggests that low RBC folate predicts low CNS MTHF levels; however, further data is needed to clarify whether low RBC levels is a sensitive predictor of response to MTHF augmentation for MDD. This data may clarify whether such indices are predictors of response to MTHF or whether MTHF may be used as an augmentation in a broader group of depressed patients.

It is of interest to note that the theoretical mechanism of the antidepressant effect of MTHF may "correct" one of many causes of low CNS MTHF that may be the primary or secondary cause of the depressive symptoms. This is consistent with the monoamine/catecholamine hypothesis of depression and genetic factors in some subtypes of depression. This indication supports the importance for clinicians to do a thorough differential diagnosis of residual symptoms that may be treated by an intervention that addresses the primary or

secondary factors contributing to depressive symptoms attributed to low CNS MTHF.

Several studies have demonstrated a relationship between low levels of folate to depression, cognitive dysfunction, and poor response to conventional treatments with antidepressants (19–22). Folate is a water-soluble B vitamin that is metabolized to different forms, including L-methyltetrafolate (also known as MTHF), the bioavailable form of folate (23,24). Unlike folate, which is the form that is provided in foods, vitamin supplements, and the supplementation of foods in many countries, MTHF is able to cross the blood-brain barrier into the cerebrospinal fluid (23,24). MTHF is essential in the synthesis and release of dopamine, norepinephrine, and serotonin and binds to presynaptic glutamate receptors, which further modulates the release of monoamine neurotransmitters in the brain (25,26). Additionally, MTHF combines with the amino acid homocysteine and vitamin B_{12} to produce *S*-adenosyl-L-methionine (SAMe), an essential methyl donor for the synthesis of dopamine, norepinephrine, and serotonin (27–31).

There are several factors that can contribute to reduced folate or the inability to convert folate into the bioavailable form of MTHF to pass through the blood-brain barrier, resulting in several potential consequences, including anemia, increased homocysteine (associated with depression, dementia, cardiovascular disease, some forms of homocysteine-dependent adenocarcinomas), neural tube defects, and depression (32–36). Other than inadequate dietary intake of folate, other possible factors that can lower folate levels or interfere with the conversion to MTHF include iatrogenic causes (anticonvulsants, oral contraceptives, lithium, lipid-lowering medications, sulfasalazine, methotrexate), certain illnesses (diabetes mellitus, Crohn's disease, atrophic gastritis, ulcerative colitis, hypothyroidism, leukemia, renal failure), pregnancy, alcohol, tobacco, emotional stress, oxidative stress, and certain common genetic polymorphisms that interfere with the conversion of folate to the bioavailable MTHF (33,37–41). The genetic polymorphism C677T mutation of the enzyme (MTHF transferase) responsible for impairing the metabolism of folate to MTHF has been associated with increased homocysteine levels and increased rates of depression compared with the general population (41–49). One study showed that 70% of their depressed population tested positive for the C677T polymorphism (14% homozygotes and 56% heterozygotes), which means that they are generally able to produce less bioactive MTHF (45). This relative insufficiency could result in less monoamine synthesis and predispose to depression.

Several trials with monotherapy folate demonstrated folate to be effective and well tolerated, although the best dose and form of folate remain unclear. Guaraldi et al. treated 20 geriatric patients with depression with 50 mg/day of open-label MTHF for six weeks and observed a significant reduction ($p < 0.0001$) in depressive symptoms on the 21-item HAM-D (HAM-D-21), with no reports of significant adverse events (50). DiPalma et al. reported on 36 patients with MDD and alcohol dependence treated with 90 mg/day of MTHF for four weeks and showed improvement ($p < 0.01$) in their depressive symptoms based on HAM-D-21 criteria and experienced no significant side effects (51). Another multicenter study of 96 patients with depression and dementia found that patients experienced improvements ($p < 0.05$) in depressive symptoms on the HAM-D after receiving 50 mg/day of MTHF for eight weeks. These patients also experienced a significant improvement ($p < 0.05$) in cognition (measured as

immediate recall) (52). This study had a comparison group treated with trazodone 100 mg/day; both groups reported similar antidepressant effects; however, the trazodone group failed to show the improvement of cognition reported in the MTHF group (52). Although further definitive placebo-controlled data are needed and likely ongoing, initial studies indicate that folate monotherapy may be a safe and effective option for the treatment of depression in potential MDD subtypes or those vulnerable to medication-related adverse events.

The use of folate or MTHF has been studied as an augmentation in several studies. Coppen and Bailey conducted a study in which patients with major depression were randomly assigned to receive either 500 μg/day of folic acid ($n = 62$) or placebo ($n = 65$) in addition to 20 mg of fluoxetine from the start of treatment (53). The outcomes showed that adjunctive folic acid rather than placebo allowed a greater response to fluoxetine and reported fewer adverse events. Godfrey et al. reported on patients with MDD ($n = 24$) who were folate deficient and given 15 mg/day of MTHF in addition to psychotropic treatment (54). These patients experienced a greater reduction of symptoms compared with patients receiving a placebo augmentation (54).

Alpert et al. reported on 22 patients who had experienced only partial response or nonresponse to at least four weeks of antidepressant treatment (55). After eight weeks of augmentation with 15 to 30 mg/day of leucovorin, a form of folinic acid that is converted into MTHF, the sample experienced a significant reduction in depressive symptoms, although only 19% reached remission (55). Subjects in this study were not folate deficient at baseline. Another study reported that folate augmentation enhanced lithium response in patients being treated for bipolar and unipolar depression (56). A substantial number of these subjects ($n = 75$) had low folate levels at baseline. After receiving 200 μg/day of folic acid in addition to lithium for one year, the patients with higher end-of-trial folate levels (13.0 ng/mL or greater) experienced a 40% reduction in their affective morbidity (56).

Considering the favorable safety and tolerability, initial evidence of efficacy as a monotherapy in some depressive subtypes, and increasing evidence as an augmentation, the use of MTHF can be considered in a range of depressive subtypes. The current indication for augmentation in partial responders with low serum or RBC folate may expand to a broader range of depressed patients pending the outcome of studies currently in progress. Given the "recognized" indication as a medical food augmentation, MTHF can be considered early as a choice for augmentation at any stage of treatment when there is an incomplete or sustained incomplete remission of the depressive disorder. MTHF can be considered early in the course of treatment for patients at high risk for low MTHF (e.g., genetic polymorphism, low serum folate or RBC folate levels, or risk factors associated with low folate or MTHF—iatrogenic factors, lifestyle factors, or comorbid illness associated with this risk). Our group commonly uses MTHF in depressed unipolar or bipolar depressed patients on anticonvulsants or lithium, even for prophylactic effects to avoid further MTHF depletion. Given favorable tolerability/safety, a trial of MTHF may be attempted before proceeding with potentially costly laboratory tests for serum and RBC folate, genetic testing for polymorphism or homocysteine levels. On the other hand, baseline RBC folate or homocysteine levels may provide a "gauge" to monitor these indices and their correlation with changes in depressive or cognitive symptoms. The additional benefits on cardiovascular and hypothetical

"neurological" protective effects are additional potential benefits of this augmentation strategy.

The recommended dose of MTHF (Deplin) is 7.5 mg once a day. Current studies may help clarify whether higher doses may be beneficial in some patients. Our group routinely allows 4 to 12 weeks to ascertain antidepressant effects and will consider increasing the dose to 15 mg/day especially if 7.5 mg/day provides partial effect and/or the patient has high risk factors for reduced MTHF or folate. Further studies may provide further information on the optimal use of MTHF as an augmentation or possible monotherapy in subtypes of depressed patients.

Lithium

Since the serendipitous discovery of the use of lithium as a mood-stabilizing compound in 1948, few individual psychotropics have been able to match lithium's contribution to biological psychiatry. From one of the latest FDA approvals for MTHF, we will now move to one of the best-studied, outcome-based strategies for treating resistant depression, which is lithium augmentation.

The antidepressant mechanism of lithium is thought to result from the potentiation of the sensitization on the postsynaptic serotonergic receptors and from the presynaptic enhancement of serotonin transmission by lithium (57). Other hypotheses include effects on monoamine receptor sensitivity, simple additive effects of two antidepressants, lithium's effect on noradrenergic and dopaminergic systems, and promotion of neuronal health and growth factors (58).

The literature is full of studies documenting the effect of lithium on TCA-resistant depression. The first report of adjunct lithium in the treatment of TCA-resistant depression comes from deMontigny et al. (59), who conducted an open, uncontrolled study of unipolar depressives. The response to lithium potentiation was reported to be dramatic and occurred within 48 hours of its initiation. Since this report, there have been numerous uncontrolled studies or anecdotal reports on the effectiveness of lithium in TCA-resistant patients. Many results from later double-blind, controlled studies subsequently supported the data from the previous studies (57,58). One study evaluated the effects of lithium potentiation on TCA compared with placebo to rule out direct antidepressant effects of lithium; the results support the hypothetical synergism of lithium and TCA, rather than the antidepressant effects of lithium alone (57). However, in both of these studies, the small number of subjects is among the methodological shortcomings (60).

Lithium augmentation for psychotic depression is reported in the literature. Several case reports suggest the efficacy of lithium potentiation in either TCA or TCA/neuroleptic treatment failures (61–63). As suggested in antidepressant monotherapy with lithium, a more favorable efficacy of lithium augmentation is suggested in bipolar rather than unipolar depressives (61). The utilization of lithium potentiation in depressive geriatric patients who are either unresponsive to conventional treatment or who cannot tolerate the side effects of increased doses of TCAs is reported to be beneficial (64,65). A review of the literature reports no significant synergistic adverse events from the combination of TCA and lithium.

With the beginning of a new era in the treatment of depressive disorders in the early 1980s, lithium quickly became one of the most accepted choices of

augmentation to SSRIs and, subsequently, SNRIs despite most evidence being related to lithium plus TCA. As a result, the literature is full of case reports, open-label studies, retrospective analyses, and some randomized, controlled trials on the subject matter. To be fair, the majority of patients included in studies where lithium was added to the conventional antidepressant medication are classified as "treatment failures" on the primary antidepressant medication, or "treatment resistant"/"treatment refractory." As a result, methodological drawbacks make it difficult to compare patient populations with those studies that are simply evaluating the efficacy of a primary antidepressant medication.

A review of 23 controlled and uncontrolled studies evaluating the efficacy of monotherapy with lithium for the treatment of depression suggests that lithium has reasonable antidepressant properties (66). Unfortunately, many of the studies have methodological flaws that fail to uniformly select for previous failures to other treatments.

Bauer et al. reviewed 27 studies, including double-blind, placebo-controlled, randomized-comparator, and open-label trials, and a total of 803 patients with refractory depression were augmented with either lithium or placebo (67). In the acute-treatment trials, the average response rate in the lithium-augmented group was 45% versus 18% in the placebo-controlled (67) one. The trials noted that lithium augmentation should be continued for a minimum of 12 months (67). Unfortunately, only a few placebo-controlled trials examined lithium's efficacy with SSRIs or other antidepressants (67).

With particular interest on remission, Bauer et al. conducted a four-month randomized, parallel-group, double-blind, placebo-controlled trial of lithium augmentation during the continuation treatment of 30 patients with a refractory major depressive episode who had responded to acute lithium augmentation during a six-week open study (68). Relapses (including one suicide) occurred in 47% of patients who had received placebo in addition to antidepressants (68). None of the patients who received lithium suffered a relapse (68).

Nierenberg et al. conducted a systematic follow-up of depressed patients with documented refractoriness to antidepressants treated with lithium augmentation (69). Sixty-six patients were followed in a retrospective, naturalistic design for 29 months to assess their longitudinal course (69). At follow-up, 29% had poor outcomes (e.g., hospitalization, suicide/death or attempt), 23% fair outcomes (return of depressive symptoms only after two weeks), and 48% had good outcomes (did not meet criteria for poor or fair) (69). An important finding in this report suggested that an acute positive response to lithium augmentation predicted a good maintenance course (69).

The more recent data from STAR*D assessed the efficacy of lithium versus triiodothyronine (T_3) augmentation in those who failed to achieve an adequate response, remission, or intolerance at level 2 (Fig. 1) (3,5). One hundred and forty-two subjects were randomized to lithium ($n = 69$) or T_3 ($n = 73$) augmentation. Forty-three percent of subjects were still on the SSRI (citalopram), and the remaining subjects were on either bupropion SR, venlafaxine extended release (ER), or sertraline. Remission occurred in 13.2% of the lithium group and 24.7% of the T_3 group; there was no statistically significant difference between the two groups and no difference between the four different antidepressant groups in overall remission. There were higher dropout rates for side effects in the lithium group compared with that of T_3. Of the subjects who achieved

remission with lithium augmentation, 55% remitted by week 4 and 66% by week 6. Similarly, for T_3 augmentation, 45% achieved remission by week 4 and 67% by week 6. Lithium was initiated in this trial at 450 mg/day with the goal to reach 900 mg/day (in divided doses) by week 2. T_3 was initiated at 25 μg/day for one week and increased to 50 μg/day by week 2 (3,5). This data supports the efficacy of lithium augmentation to SSRIs—venlafaxine ER or bupropion SR—in a group of patients who failed to adequately remit to at least two levels of treatment (3,5).

Choosing lithium as an augmentation strategy to an antidepressant medication can be challenging. Despite lithium's well-documented augmentation data regarding efficacy, it is also associated with potential tolerability issues. In addition, truths and misconceptions regarding lithium have developed throughout the years of its use. With the availability of a large and growing number of treatment strategies, it is not uncommon for patients to associate lithium with negative misperceptions as an older, less commonly used medication. Therefore, it is crucial that the clinician addresses these issues to increase patient comfort.

Although dosing strategies need to be clarified, augmentation can be carried out initially with 300 to 450 mg at bedtime, increasing to a range between 600 and 1200 mg/day in twice-daily dosing within two to three weeks. While clinical correlation is best in determining efficacy, checking a pre-dose morning lithium level approximately four to five days after the last adjustment is warranted. A typical "therapeutic window" for lithium is between 0.8 and 1.2 in the treatment of bipolar disorder, although significantly lower levels might be effective in unipolar depression when lithium is added to an antidepressant. Lithium's negative effects on organ systems include its ability to impede the release of thyroid hormones, to impair cardiac sinus node function and the urine concentrating mechanism of the kidneys (70). As a result, the clinician should perform routine laboratory testing, including serum creatinine concentrations, electrolytes, thyroid function, a complete blood count, electrocardiogram, and a pregnancy test in women of childbearing age (70). It should be noted that lithium may be quite useful in the treatment of a depressed patient with a history of "soft" bipolar symptoms or a family history of bipolarity. Our group also considers lithium augmentation in patients with suicidal ideation, and consistent with reports in the literature, a direct or indirect protective effect on suicidal ideation may exist.

There is an extensive literature on the use of lithium, suggesting positive, acute, and long-term efficacy. The use of lithium remains among the most well-documented augmentation strategies in a treatment-resistant/treatment-refractory patient. However, more randomized, controlled trials are needed to assess the efficacy of lithium potentiation, especially with newer antidepressants. In addition, more data are needed on dosing acutely and chronically, duration of treatment, and the addition of lithium to unique present-day first-line strategies.

Thyroid Hormone

For over a century, it has been reported that depression is associated with thyroid abnormalities. Both hypo- and hyperthyroid states are correlated with affective disturbances, and this correction of the underlying thyroid dysfunction often alleviates affective symptoms. This association has led to the utilization of

thyroid hormones in the treatment of depression. The first studies examining the effects of thyroid hormones in depression were conducted in the 1950s and showed an improvement in the symptoms following the use of T_3 (71,72). In 1969, Prange et al. (73) reported on the effects of thyroid hormones in depression using controlled, double-blind designs. Results suggest shortening the latency until TCA action (at least in women) and effective antidepressant activity in TCA-resistant patients (men and women). Replication of these findings shows that the addition of thyroid hormone to TCA in euthyroid patients can increase the efficacy of TCAs and accelerate the onset of action (74–76). Many reports on uncontrolled studies in the 1970s are suggestive of TCA/T_3 combination being effective in a substantial number of patients who were unresponsive to monotherapy with a TCA. The usual dose of T_3 was 25 μg/day, and imipramine and amitriptyline were the TCAs most often used (77–81). Goodwin et al. (82), in a double-blind but not placebo-controlled study, reported that depressed patients unresponsive to TCA benefited from the addition of T_3. Thase et al. (83) reported on a sample of 20 depressed outpatients who were unresponsive to 12 weeks or more of imipramine administration, as well as to potentiation of imipramine with T_3 at 25 μg/day. This study did not validate the previous findings.

Sokolov et al. reported a nonrandomized study of 24 patients without placebo control (84). Thyroid function was measured before antidepressant treatment following the failure of acute desipramine treatment but before T_3 augmentation (84). T_3 augmentation responders were found to have lower levels of thyroid stimulating hormone (TSH) (2.36 ± 0.75 vs. 3.29 ± 0.88) and higher levels of T_4 and free thyroxine index (FTI) than nonresponders (35.25 ± 4.63 vs. 29.92 ± 6.60) (84). After antidepressant failure, prior to augmentation, TSH was lower in patients who went on to respond to T_3. The findings suggest that T_3 augmentation response is associated with lower levels of TSH and elevations in the levels of T_4 and FTI present before antidepressant treatment (84).

Aronson et al. completed a meta-analysis of eight studies and 292 patients addressing the efficacy of liothyronine sodium therapy in euthyroid, nonpsychotic depressed patients refractory to TCA therapy (85). Patients treated with liothryonine sodium augmentation were twice as likely to respond compared with controls. This corresponded to a 23.3% improvement in response rates and a moderately large improvement in depression (85).

Joffe et al. completed a two-week, randomized, double-blind, placebo-controlled study of 50 patients with unipolar depression refractory to desipramine or imipramine, by comparing the efficacy of lithium and liothyronine as augmenting agents (86). Both the augmenting agents were more effective than placebo in reducing HAM-D scores, although there were no statistically significant differences between lithium (9 out of 17 responded) and liothyronine (10 out of 17 responded) (86).

In another study, Joffe and Singer completed a three-week, 40-patient, randomized, double-blind study in which subjects who had failed a trial of imipramine or desipramine were given either T_3 or T_4 in addition to their antidepressant (87). Fifty-three percent of subjects responded to T_3, whereas 19% responded to T_4 (87). This study would suggest that the T3 hormone may be a better choice as an augmenting agent.

There are three reported cases in the literature of MAOI/T_3 combination efficacy in MAOI-resistant depression. The first report involves a rapid alleviation of depressive symptoms when T_3 was added to a combination of phenelzine and

thiothixene in a woman who had blunted TSH response to thyroid releasing hormone (TRH) stimulation (88). The other report involved amelioration of depressive symptoms in two patients after T_3 was added to phenelzine, or phenelzine and lithium (89). Further controlled studies are needed to clearly define the safety and efficacy of thyroid hormone enhancement in MAOI-refractory depression.

The recent data from STAR*D supporting comparable efficacy to lithium at the third level of treatment is described in the previous section on lithium augmentation (3,5).

Nearly all of the reports of using T_3 in doses between 25 and 50 μg/day added to TCAs have found this combination to be safe. There are no reports of increased serious side effects caused by the individual agents or any unusual side effects (73,81,82). T_3 does not have any apparent effect on the TCA blood levels (90). T_3 has the potential to be associated with cardiotoxic effects, and the use of catecholamine-enhancing antidepressants has increased cardiovascular effects in hyperthyroid states. With this stated, the combination of TCA and T_3 in therapeutic doses does not appear to have notable adverse effects on cardiac function (81,82). Additionally, long-term use may be associated with an increased risk of osteoporosis (16).

The mechanism of T_3 in potentiating antidepressant response is speculative. Other proposed mechanisms of the TCA/T_3 antidepressant combination include synergism between T_3 and catecholamines. Another mechanism suggests that thyroid hormone increases the sensitivity of the noradrenergic β receptors and thus improves the existing pool of catecholamines thought to be underactive at the onset of depression (91). It is suggested that depression may be characterized by changes in the hypothalamic-pituitary-thyroid axis. While overt hypothyroidism is not commonly found in depressed persons, occult thyroid abnormalities may be present in approximately 25% of depressed persons, based on a blunted TSH response to TRH stimulation (92).

Buspirone

Buspirone is a novel anxiolytic with agonist properties at the $5HT_{1A}$ receptor and possible activity at the $5HT_2$ receptor, as well as the D2 receptor (15). Although it is used primarily in the treatment of generalized anxiety, buspirone has been considered a safe alternative in the treatment of depressive disorders (15,93). The efficacy of buspirone as a monotherapy for depression with comorbid generalized anxiety disorder (GAD) in doses up to 90 mg/day has been demonstrated (94,95). Buspirone has also been used to reduce SSRI-induced sexual dysfunction on the basis of the hypothetical role of modulating an imbalance of serotonin, dopamine, and norepinephrine (96).

Landen et al. conducted a four-week, 119-patient, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in the treatment of patients with treatment-refractory depression (97). A total of 50.9% of patients in the buspirone group and 46.7% in the placebo group responded after four weeks of treatment (97). While the study was limited by some methodological drawbacks, there was no statistically significant difference between treatment groups. However, 69.4% of the patients responded in the post-study treatment phase with an SSRI plus buspirone (97), and there were no reported statistically significant differences in the frequency of adverse effects (97).

Appelberg et al. completed a placebo-controlled, randomized, double-blind, placebo wash-in study of 102 outpatients who had failed to respond to an SSRI for a minimum of six weeks (98). These patients were assigned to either placebo or buspirone (10–30 mg twice daily) augmentation for six weeks. At the end point of the study, it was found that there was no significant difference between buspirone and placebo (98). Patients with initially high Montgomery-Asberg depression rating scale (MADRS) scores (>30) showed a greater reduction ($\rho = 0.26$) in the buspirone group compared with those in the placebo group 98). No significant side effects were noted in either the placebo or the buspirone group 98). A limitation of this and the previous study may be that of small sample size in that more successful modern day augmentation strategies, that is, aripiprazole's FDA approval, utilized a sample size twice this size.

The recent data from STAR*D provided information on the second level of treatment (Fig. 1) on the use of buspirone augmentation compared with bupropion SR combination treatment or CBT augmentation to citalopram after a patient fails to adequately respond/remit to monotherapy. This was the first level of switch/augmentation/combination offered to any patient who either showed inadequate response/remission or was unable to tolerate a 14-week trial of citalopram during level 1 (3–5). Two hundred and eighty-six patients were randomized to buspirone augmentation (maximum dose 60 mg/day in divided doses), 279 patients were randomized to bupropion SR combination (maximum dose 400 mg/day in divided doses), and 85 patients were randomized to CBT augmentation (3,4). All three groups showed similar (not statistically significant difference) remission rates 26.9% (buspirone plus citalopram), 31.8% (bupropion SR plus citalopram), and 29.4% (CBT plus citalopram) (3,4). There were higher dropout rates for the buspirone augmentation group (20.6%) compared with bupropion SR combination (12.5%) and CBT augmentation (10.5%) (3,4). Of interest, the frequency of concomitant anxiolytic and hypnotic medication was similar between the two medication augmentation/combination groups.

Additionally, the augmentation/combination group did better than patients who had the citalopram stopped and switched to another antidepressant at this level (3,4). This later observation may be explained by several factors including patients choosing augmentation/combination over switching or greater tolerability and lower HAM-D scores to level 1 monotherapy citalopram compared with patients choosing a switch option. Our group also believes that there may also be a group of patients who may become more "resistant to treatment" when switching (stopping one medication and starting a new treatment) rather than when augmenting/combining treatment to an incomplete response/remission.

While it is necessary to further study buspirone for potential antidepressant effect, it may be of great value for its safety and low incidence of adverse effects. In addition, this medication may be considered for use in patients who have residual or comorbid anxiety symptoms or iatrogenic sexual dysfunction associated with the use of the primary antidepressant.

Lamotrigine

Lamotrigine is currently FDA approved for use in the prevention of relapse/recurrence of both mania and depression in bipolar disorder patients (99). Additionally, lamotrigine may be efficacious either as a monotherapy or as an

augmentation for depression—either bipolar or unipolar subtypes—and has shown efficacy in lengthening time to relapse into a depressive episode in individuals diagnosed with bipolar disorder at a dose of 200 mg/day (99). Its favorable adverse effect profile has catapulted this treatment into the realm of antidepressant augmentation and, in some cases, has been used successfully as a monotherapy in the treatment of depressive disorders. With this stated, lamotrigine has little published randomized, placebo-controlled data in the area of treatment of unipolar depression. Theoretically, lamotrigine makes sense in that it modulates glutamate and other transmitters increases plasma serotonin levels and is a weak inhibitor of $5HT_3$ receptors (100).

Barbee and Jamhour conducted a retrospective chart review of lamotrigine augmentation (for an average of 41.8 weeks; average dose 112.90 mg/day) in 37 individuals with chronic or recurrent unipolar major depression who had failed to respond adequately to at least two previous trials of antidepressants (101). On the basis of intent-to-treat analysis, response rates were 40.5% much or very much improved, 21.6% mildly improved, and 37.8% unchanged (101). Normann et al. evaluated lamotrigine as adjunct to paroxetine in acute depression in a placebo-controlled, double-blind study in 2002 (102). Forty patients with a depressive episode by DSM-4 criteria received lamotrigine up to 200 mg/day, or placebo, in conjunction with paroxetine. While adjunctive treatment with lamotrigine did not result in a significant difference in HAM-D total score at end point compared with paroxetine and placebo, lamotrigine demonstrated significant reductions in core depressive symptoms (depressed mood, guilt feelings, work, and interest). In addition, patients receiving lamotrigine had fewer days on treatment with benzodiazepines and fewer withdrawals for treatment failure. The results of these two studies suggest that lamotrigine may be efficacious as an augmentation agent, especially in patients with shorter-duration depression and fewer antidepressant trials (101), and may accelerate the onset of action when given in combination with antidepressants (102).

These results must be evaluated cautiously in light of additional studies of lamotrigine monotherapy. Calabrese et al. published an analysis of five double-blind, placebo-controlled trials of lamotrigine monotherapy in bipolar depression in 2007 (103). Adult subjects with bipolar I or II disorder experiencing a depressive episode were randomized to placebo or lamotrigine monotherapy with doses ranging from 50 to 200 mg in four studies and 50 to 400 mg in one study. Lamotrigine did not differ from placebo on primary efficacy end points (HAM-D-17 item, MADRS) in four out of five studies.

In considering lamotrigine for the treatment of either bipolar or unipolar depression, doses as low as 50 mg may provide efficacy with additional benefit, with a target dose of 200 mg/day. The usual treatment regimen guidelines for bipolar disorders is 25 mg/day, with increases of 25 to 50 mg every two weeks toward a target dose of 200 mg/day (99). While lamotrigine is generally well tolerated, patients need to be educated about the risk of potential rash and Stevens-Johnson syndrome (99). This drug must be dosed carefully, and precisely, in these drug interactions with oral contraceptives, carbamazepine, valproate, oxcarbazepine, as well as atypical antipsychotics such as aripiprazole and risperidone, may occur. Lamotrigine's role in the treatment of the depressed patient who has "soft" symptoms of bipolarity such as persistent recurrent depression or a family history of bipolar disorder should be considered. This

agent, like buspirone, appears to have weak but some positive effect sizes and offers low risk of day-to-day side effects when considering risk-benefit analyses.

Stimulants

It has long been known that stimulants such as amphetamine, methylphenidate, and pemoline have mood-elevating effects. Amphetamine is an indirect-acting sympathomimetic agent with some direct agonist properties, which exerts its stimulant properties via direct neuronal release of dopamine and norepinephrine, blockade of catecholamine reuptake, and weak monoamine oxidase inhibition (104). Methylphenidate is structurally and mechanistically related to amphetamine (105), and pemoline is a stimulant hypothesized to augment catecholamine transmission (105).

A review of the use of stimulants in the treatment of depression demonstrates several uncontrolled reports and little controlled data supporting the antidepressant effects of this treatment, either as monotherapy or as an augmentation strategy. The data appear to support stimulants more as an augmentation rather than a monotherapy for depression (16,106).

Augmentation of TCAs with methylphenidate is suggested to be effective in rectifying TCA monotherapy failures (107). This suggestion is based on the report of five out of seven TCA-resistant patients failing an adequate trial of either imipramine or nortriptyline when methylphenidate was added at a dose of 20 mg/day (107). However, one patient experienced a manic episode, and another died from a cerebral vascular accident after two years on the combination (107). While several patients in this report showed an increase in the TCA level, which may account for the antidepressant mechanism of the combination, the antidepressant mechanism may also be accounted for by an additive or synergistic effect.

Additionally, uncontrolled reports suggest efficacy of augmenting TCA partial responders with dextroamphetamine (5–20 mg/day) (108).

The combination of MAOIs with stimulants in treatment-resistant depression is frequently avoided following reported cases of hyperthermic and hypertensive crises (some fatal) cited in the literature (109–112). However, there is more recent evidence that the combination of MAOIs and stimulants may prove to be both safe and effective in treatment-resistant patients when used properly. Feighner et al. (113) treated 13 patients with intractable depression who responded to the addition of amphetamine or methylphenidate to an MAOI with or without a TCA. Clinically significant side effects included orthostatic hypotension and, in three patients, anxiety, restlessness, agitation, or irritability (113). Two patients complained of dizziness, nausea, impairment of short-term memory, and insomnia, while one patient developed hypomania (113).

Our group reported a retrospective, naturalistic study of 32 treatment-resistant patients who were augmented with either pemoline (no longer available) or dextroamphetamine after a partial or complete nonresponse to an adequate trial of an MAOI for a mean time of 22.3 months (114). On the basis of Clinical Global Impression (CGI) scores, 78% of the 32 patients had a good response to at least one stimulant plus MAOI, with 53.8% reporting being "very much" or "much improved" (114). It should be noted that 3 out of 32 patients developed manic episodes (114). There was no evidence of serious adverse events. It should be noted that these papers should be referenced carefully to use

this combination because there is a risk of hypertensive crisis if inaccurate application is used.

In the attempt to avoid the typical two- to four-week latency associated with TCAs, Gwirtsman et al. conducted a three- to four-week, open-label trial of 20 depressed patients in which both TCA therapy and methylphenidate were started concurrently (115). By the end of week 1, 30% of the patients responded to the TCA + methylphenidate hydrochloride and 63% responded by the end of week 2 (115). Ultimately, 85% demonstrated improvement on the basis of CGI scores at the time of discharge (115).

These studies were uncontrolled and used concomitant psychotropics, including TCAs, thyroid enhancement, lithium, and other mood stabilizers. It is possible that the safety of adding a stimulant to an MAOI may be enhanced with concomitant use of a TCA, because there is evidence that the use of amitriptyline may protect against potential tyramine reactions (116), however, not all of the patients were on TCAs in these trials.

There is a report in the literature of one case using amphetamine to potentiate the antidepressant effects of fluoxetine (117). The patient failed to respond to imipramine potentiated with amphetamine (45 mg three times a day). He subsequently responded to a combination of fluoxetine (60 mg/day) and amphetamine (45 mg three times a day). Relapse of depressive symptoms was reported with attempts to discontinue the amphetamine.

We reported eight patients who had been given methylphenidate (10–40 mg/day) in addition to fluoxetine (20–80 mg/day), with a sustained antidepressant response for at least six months in two patients (16). In addition, we reported on a case where pemoline (37.5 mg twice a day) was added to fluoxetine (80 mg/day), with a sustained antidepressant response in one patient who had failed a number of other adequate antidepressant trials, some of which included pemoline potentiation. None of the cases combining either methylphenidate or pemoline had adverse events. The use of stimulants for medically ill, depressed patients in uncontrolled reports indicates a potential therapeutic role for this population of patients (104). Finally, evidence indicates that the use of stimulants may combat the hypotensive effects of conventional antidepressants (107).

On the whole, the use of stimulants in the treatment of depression demonstrates little evidence of tolerance (104). Our own experience with the use of stimulants also suggests little evidence for abuse potential when used judiciously. The use of stimulants plays a very important potential role in the treatment of depressive disorders, particularly in patients with treatment-resistant depression and depression associated with low energy, anhedonia, and comorbid attention-deficit hyperactivity disorder (ADHD). Obviously, well-controlled studies are needed to elaborate on their potential safety and efficacy.

Atypical Antipsychotics

There is a growing literature on the use of atypical antipsychotics as augmentation to an antidepressant medication. Atypical antipsychotics act primarily by blocking the D_2, $5HT_{2A}$, and $5HT_{2C}$ receptors. They may also modulate, in varying degrees, several additional serotonin sub-receptors (such as $5HT_3$, $5HT_{1B}$, $5HT_{2B}$) and inhibit the reuptake of norepinephrine and serotonin. Each drug in this class possesses a unique receptor profile, which can help the

physician pick the appropriate therapy for an individual patient. Some of the above mechanisms at serotonin sub-receptors also apply to certain FDA-approved antidepressants (e.g., mirtazapine, nefazodone, trazodone), increasing the possibility that the atypical antipsychotics may be effective treatments for anxiety and depression.

Barbee et al. conducted a retrospective chart review of 76 medication trials in 49 patients to determine the effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone as augmentation agents in patients with treatment-resistant depression (118). The overall response rate was 65%. The difference between baseline and final global assessment of functioning (GAF) scores was statistically significant only in the olanzapine (57%) and risperidone (33%) groups (118). With regard to side effects, it was found that weight gain was associated with olanzapine; nausea, anxiety, and depression were associated with risperidone; and sedation was associated with quetiapine and ziprasidone (118).

The net result of $5HT_{2A}$ antagonism is the reversal of D2 blockade in the nigrostriatal pathway [responsible for extrapyramidal symptoms (EPSs)], the tuberoinfundibular pathway (responsible for hyperprolactinemia), and the mesocortical pathway (responsible for negative symptoms). This differentiates the atypicals from conventional antipsychotics and greatly improves the side effect profile and likelihood of treating depression. This blockade may facilitate serotonergic activity compared with conventional antidepressants and may allow for mesocortical dopaminergic/noradrenergic activity to actually increase. While there may be individual risk factors, as well as differences between the atypical antipsychotics, they are all associated with a potential risk of metabolic adverse events. Possible type II diabetes mellitus (glucose intolerance, insulin resistance), increased lipids, and weight gain are some examples of the potential risk of developing "the metabolic syndrome" associated with some agents in this new class of drugs. While increasing data suggest that the use of some atypical antipsychotics appears to cause a higher incidence of these problems, it is uniformly recommended to monitor metabolic parameters at baseline and regular intervals with all atypical antipsychotics set forth in guidelines by the American Psychiatric Association and American Diabetes Association (119). With regard to the above-stated suggestion, the clinician must use careful judgment in the administration of these drugs in combination with antidepressant medications, coupled with patient education and regular monitoring. Moreover, because these are dopamine-blocking drugs, the typical warnings exist for the monitoring of all extrapyramidal syndromes.

Olanzapine

Tohen et al. initially reported that olanzapine monotherapy, or in combination with fluoxetine, produced a greater reduction of core depressive symptoms (e.g., sadness, pessimism, suicidal ideation) compared with placebo in bipolar I depressed patients (120). Both groups showed similar statistically significant differences in core depressive symptoms.

Shelton et al. conducted an eight-week, randomized, double-blind trial of 28 patients with treatment-resistant unipolar depression to assess the efficacy and safety of olanzapine with fluoxetine versus either agent alone (121). Olanzapine plus fluoxetine produced significantly greater improvement than either monotherapy from baseline, MADRS (combination, 13.6; olanzapine, 2.8;

fluoxetine, 1.2), or CGI (combination, 2.0; olanzapine, 0.0; fluoxetine, 0.4) (121). Increased appetite and weight gain occurred significantly among patients treated with olanzapine. There were no significant differences between treatment groups with regard to EPSs or adverse drug interactions. Thase et al. replicated these findings in a group of unipolar depressed patients (122), yet subsequent trials failed to replicate the findings (123,124). Recently, olanzapine-fluoxetine combination was FDA approved for treatment resistant depression.

Risperidone

Hirose and Ashby completed a six-week, 36-patient, open-pilot study of fluvoxamine plus risperidone as an initial antidepressant therapy (125). Among the study completers, 76% achieved remission (vs. 20–30% remission rate of six-week SSRI treatment), 17% achieved response, and two were not responsive (125). Adverse effects were mild, without cases of EPSs, nausea, or vomiting (125). Two subsequent studies were reported that showed risperidone's efficacy in patients who failed to respond to monotherapy SSRI (126,127).

Ziprasidone

In an open-label trial conducted by Papakostas et al., 20 patients with MDDs who had failed to respond to an adequate trial of an SSRI were treated with ziprasidone for six weeks (128). At the end of the trial, 61.5% were classified as responders with 38.5% remittance. Intent-to-treat analysis showed a 50% response and 25% remittance (128). The use of ziprasidone appeared safe, with no severe adverse events and no clinically significant QTc prolongation (128).

Dunner et al. reported on a group of depressed subjects ($n = 64$) who failed to adequately respond to a six-week trial of sertraline (150–200 mg/day) who were randomized to single-blind continuation of monotherapy sertraline ($n = 20$) or received ziprasidone augmentation [80 mg/day ($n = 23$) or 160 mg/day ($n = 20$)] for eight weeks (129). There was a numerically significant greater improvement in the two augmentation groups compared with the monotherapy sertraline group in mean improvement of MADRS and response rates (10% monotherapy sertraline; 19% sertraline/ziprasidone 80 mg/day; 32% sertraline/ziprasidone 160 mg/day) (129). Of note, the remission rate in the sertraline/ziprasidone 160 mg/day group was 21% and 5% for the other two groups (129).

Aripiprazole

Aripiprazole was the first pharmacological agent to receive formal FDA prescription approval (in 2007) as an adjunctive treatment for inadequate response to monotherapy antidepressant. The standards for this prescription approval are considered higher than the medical food standards applied to MTHF discussed earlier. In addition to the 5HT modulating effects via the $5HT_2$ blockade and $5HT_{1A}$ stimulation of these receptors, aripiprazole has a unique pharmacological property as a "partial" dopamine agonist as well. The antidepressant mechanism may involve a modulation of the dopamine and serotonin systems, allowing for these neurotransmitter systems to work and adapt to any changes to either system.

Our group reported on the augmenting effects of aripiprazole to poor responders to SSRI or venlafaxine ER monotherapy for unipolar depression (130).

We conducted an open-label, efficacy and tolerability trial of aripiprazole augmentation in 10 TRD patients with incomplete response to a prior, adequate trial of an SSRI or venlafaxine ER (unpublished data). Patients had a minimum HAM-D-17 score of 12 (mean HAM-D score 17.8) and received at least six weeks of prior SSRI or venlafaxine ER monotherapy. Aripiprazole augmentation was given in a flexible-dose fashion ranging from 7.5 to 30 mg daily for eight weeks. The primary outcome measure was a $\geq 50\%$ reduction in HAM-D-17 score over time. Additional outcomes included the CGI/C, MADRS, Hamilton rating scale for anxiety (HAM-A), and Barnes akathisia scale (BAS) (130) ratings. Mean HAM-D score at end point was 7.0 (mean change in HAM-D total score –10.8). A similar reduction in baseline scores through end point was found with the HAM-A, MADRS and CGI/C. There was a significant worsening of the BAS at weeks 1 and 2, and then no change from baseline after week 4. While the BAS showed akathisia occurring in the first weeks of aripiprazole treatment, it dissipated by the fourth week of treatment. There were no treatment discontinuations as a result of akathisia. The mean end point dose of aripiprazole was 12.4 mg/day. There were no clinically meaningful changes in vital signs, QTc interval, weight, or chemistry values from baseline to end point. This open-label study showed that aripiprazole augmentation may be an effective antidepressant therapy for TRD with additional anxiolytic benefit occurring within the first week of treatment. The akathisia reported early in the course of treatment dissipated over time. It may have been associated with high initial aripiprazole doses.

Well-conducted, stringent, randomized, controlled trials have shown efficacy of aripiprazole as an augmentation agent and less often as a monotherapy in patients with treatment-resistant depression (131–137). These studies have shown the onset of aripiprazole activity as early as week 1 of treatment at doses lower than those used in schizophrenia or mania. Two recent randomized, multi-site, double-blind, placebo-controlled trials have demonstrated the efficacy and safety of aripiprazole as an augmentation therapy of incomplete monotherapy, prospective treatment with an SSRI or SNRI (venlafaxine ER). These results directly led to the FDA-approved labeling of aripiprazole for augmentation (not monotherapy) use in SSRI- and SNRI-resistant MDD in November 2007 at a dose range of 2 to 15 mg/day. Both registration studies had a similar design. Berman et al. reported the results of one of these trials that involved a 7- to 28-day screening phase that confirmed TRD to three or less prior antidepressant trials using the antidepressant treatment response questionnaire (ATQR) ($n = 1044$) (138). This was followed by an eight-week study phase with single-blind adjunctive placebo ($n = 622$) and a six-week, double-blind phase of either escitalopram 10 to 20 mg/day, fluoxetine 20 to 40 mg/day, paroxetine 37.5 to 50 mg/day, sertraline 100 to 150 mg/day, or venlafaxine ER 150 to 225 mg/day plus placebo versus antidepressant plus aripiprazole. The double-blind study phase included patients who were prospectively unresponsive in the previous stage. Patients were randomized to aripiprazole 5 to 15 mg/day ($n = 184$) or placebo ($n = 178$). The dose of aripiprazole or matching placebo was allowed to be decreased to 2 mg/day for tolerability issues. The primary outcome was change in total MADRS score from the double-blind baseline. Secondary outcomes included remission and response rates and CGI/S and CGI/C ratings (among others). The mean change of MADRS score was –8.8 for aripiprazole versus –5.8 for placebo (effect size = 0.39; $p < 0.001$). Aripiprazole

efficacy of –6.3 was seen as early as week 2 (vs. –3.4 for placebo) ($p < 0.001$). Remission and response rates were also higher in the aripiprazole group versus placebo [(15.7% vs. 26.0%) ($p = 0.011$) and (23.8% vs. 33.7%) ($p = 0.025$), respectively]. Similar rates were observed for the CGI/S and CGI/C ratings (138). The mean dose of aripiprazole in this trial was approximately 11 mg/day.

Our group has found success in starting patients on low doses (occasionally only 1 mg/day) and gradually increasing the dose to minimize side effects such as akathisia.

Quetiapine

Quetiapine is amongst the most extensively studied atypical antipsychotic in the treatment of bipolar and unipolar depression. Early trials assessed quetiapine immediate release, while more recent trials have used the ER version. A unique combination of direct and indirect pharmacological actions mediated with quetiapine and its active metabolite, norquetiapine, may underpin its clinical antidepressant properties. The high affinity and inhibitory actions on the norepinephrine transporter and potent $5HT_2$ antagonism resulting in down-regulation of these receptors represent the strongest evidence to suggest the antidepressant activity of quetiapine (139).

Early open-label trials supported the efficacy of a range of doses of quetiapine to improve antidepressant efficacy in partial responders. At lower doses (<150 mg/day), the augmenting antidepressant effects of quetiapine to partial responders to monotherapy antidepressants may have been partly due to improvement of sleep, anxiety, or improving sexual function/satisfaction from the limited pharmacological effect on blocking histamine and the $5HT_2$ receptor antagonism at these doses. However, higher doses ($\geq$150 mg/day) may provide a broader pharmacological profile on the serotonin, dopamine, and noradrenergic system that may provide a more direct antidepressant effect of quetiapine (139).

Quetiapine was the first pharmacological treatment to receive FDA approval as a monotherapy for the depressed phase in bipolar I and II disorders at doses between 300 and 600 mg/day. Two randomized, controlled, double-blind, eight-week studies comparing quetiapine 300 mg or 600 mg with placebo for depression in bipolar I and II showed remission rates that were statistically superior to that of placebo over eight weeks of treatment (140,141). In these studies, the proportions of patients meeting remission criteria (MADRS $\leq$ 12) at final assessment were significantly above 50% compared with less than 30% for placebo. There were minimal differences between the 300-mg and 600-mg groups, and most of the MADRS items, including the core symptoms of depression, were significantly improved as well, showing a broad range of improvement, not just hypnotic effects. Treatment-emergent mania rates were similar to that of placebo. Common adverse events were dry mouth, sedation, dizziness, constipation, fatigue, headache, and nausea.

Two large, placebo-controlled trials also support the use of quetiapine as an adjunctive treatment for inadequate response to various antidepressants. El-Khalili et al. (142) evaluated the efficacy and tolerability of quetiapine ER as an adjunctive treatment in 446 patients with unipolar MDD who had an inadequate response to their current antidepressant treatment, in an eight-week, randomized, double-blind, placebo-controlled trial. The antidepressants included adequate

trials of amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, and venlafaxine. Patients received quetiapine ER 150 mg/day, 300 mg/day, or placebo in addition to their current antidepressant treatment. At week 6, the response rate (≥50% improvement on the MADRS) was significantly higher with quetiapine ER 300 mg/day compared with placebo (58.9% vs. 46.2%). Remission rates (MADRS total score ≤8) were significantly higher for quetiapine ER 300 mg (42.5% vs. 24.5%). Patients taking a dose of 150 mg had significant improvement on the HAM-D at week 6 but not on the MADRS. The proportion of patients who withdrew because of an AE was 10.8% (150 mg), 18% (300 mg), and 0.7% (placebo) (142). Earley et al. (143) conducted a randomized, placebo-controlled, six-week study to evaluate the efficacy and tolerability of quetiapine ER as an adjunctive treatment in 493 patients with unipolar MDD who had shown an inadequate response to their current antidepressant treatment. Patients were randomized to receive quetiapine ER 150 mg, 300 mg, or placebo in combination with their antidepressant, which were similar to that of the trial above by El-Khalili et al. Response rates (≥50% reduction in MADRS total score) were significantly higher for quetiapine ER 300 mg versus placebo (57.8% vs. 46.3%). For the 150-mg group, the response rate at week 6 (55.4%) was numerically, but not statistically higher than placebo. Remission rates (MADRS ≤ 8) were significantly higher for 150 mg (36.1%) than placebo (23.8%), but not for the 300-mg group (31.1%). Withdrawals due to AE were similar to that of the above El-Khalili study, with the most common being sedation, somnolence, and fatigue.

Our group has found quetiapine to be highly useful as a monotherapy or adjunct in the clinical setting for unipolar and bipolar depression. While doses under 150 mg/day may provide improvement on sleep, anxiety, and sexual function, higher doses may be necessary to treat the range of symptoms associated with unipolar and bipolar depressive illness. Our group may start quetiapine at the lower-dose range but increases doses toward 300 mg/day as either a monotherapy or an augmentation. Use of quetiapine ER allows for once-per-day dosing in the evenings, and clinicians need to be cognizant of less risk of acute sedation/somnolence if quetiapine is given on an empty stomach.

Our group routinely uses all of the atypical antipsychotics in combination with antidepressants from all classes in varying dosages, with good success. As with other augmenting strategies, the inherent nature or treatment profile of the drug may be helpful in the treatment of a depressive disorder. An example would be the use of an atypical antipsychotic with sedation properties to improve a case of sleep disturbance associated with depression. Another example would be the case of a depressed patient who presents clinically in a nonpsychotic fashion but may have an underlying degree of psychosis, as in delusional guilt or rumination. In addition, the inherent receptor profile of the atypical antipsychotic drugs may be reason enough to use them as an antidepressant strategy. The pharmacodynamic profile of each second-generation antipsychotic should allow reasonable serotonergic modulation.

Benzodiazepines

Over 60% of patients with depression suffer from anxiety symptoms. Residual anxiety symptoms are common yet can potentially aggravate the depression, and anxiety remains one of the greatest predictors of imminent suicide in depression. Benzodiazepines are effective anxiolytic medications offering rapid

reduction in anxiety symptoms. Many negative perceptions secondary to potential abuse can be a barrier in the use of these highly effective medications. The role of acute reduction in anxious symptoms in the treatment of depression is important. There is little data on long-term use or on the treatment of residual and/or comorbid anxiety.

Benzodiazepine augmentation may be one of the more popular strategies employed by physicians, although there is little data to support it, as well as little data to refute this strategy. If one were to consider the HAM-D, about one-third of the items on this scale would count as "anxiety symptoms," and sedatives are felt to be effective in quickly lowering these symptoms.

Furukawa et al. completed a meta-analysis of nine randomized, controlled studies with 679 adult patients who were followed for up to eight weeks to determine whether antidepressant-benzodiazepine treatment was more efficacious than treatment with antidepressant alone in treating major depression (144). On the basis of intent-to-treat analysis, the combination group was more likely, 63% versus 38%, to show response in four weeks (144).

Smith et al. completed an eight-week, double-blind, randomized study of 80 patients rated as markedly or moderately ill given fluoxetine (20–40 mg/day) plus placebo or fluoxetine plus clonazepam (0.5–1.0 mg/day) (145). Patients in both treatment groups improved over the course of the study with regard to HAM-D scores, although the change in scores was more significant in the augmentation group within the first week ($p = 0.002$), at day 10 and at day 21 ($p < 0.001$) (145). No serious adverse events were found in either treatment group. Taper effects were modest and transitory (145).

Treatment with benzodiazepines can be short term (approximately four to six weeks) or as long as clinically indicated. We suggest that clinicians collaborate with patients on dosing and frequency as a strategy in determining an appropriate schedule with additional doses as needed for "breakthrough anxiety." This needs to be balanced with abuse potential, sedation, alcohol intake, and coadministration with other central nervous system–sedating agents.

Pindolol

Pindolol is a β-adrenergic blocker that is also an antagonist and a partial agonist at $5HT_{1A}$ receptors (100). It has been theorized that pindolol can immediately disinhibit serotonin neurons, leading to the proposal that it may be a rapid-onset antidepressant, or a facilitating or augmenting agent (100). There are clinical studies that do suggest that pindolol augmentation may speed the onset of action of SSRIs, but there is little additionally supportive data (100).

Isaac conducted a 42-day randomized, double-blind, placebo-controlled study of 80 patients who were given milnacipran plus pindolol or milnacipran plus placebo (146). Improvement in MADRS total score was greater in the pindolol group from day 7 (mean change from baseline –9.6 vs. –5.3) (146). CGI improvement was significant, with 97.2% in the pindolol group and 60.6% in the placebo group (146).

Perez et al. conducted a single-blind, placebo, lead-in phase followed by a six-week, randomized, 111-patient, double-blind, parallel study with two treatment arms—fluoxetine plus pindolol and fluoxetine plus placebo (147). At end point, the response rate in the fluoxetine-plus-pindolol group and percentage of remitted patients were 15.6% and 15.4% greater than that in the placebo arm,

respectively (147). The median time to sustained response with pindolol was significantly reduced when compared with that of placebo (19 days vs. 29 days) (147). There was no difference in side effects between the two groups in this study (147).

Perez et al. conducted a six-week, double-blind, randomized, placebo-controlled trial of pindolol augmentation in 80 depressive patients resistant to SSRIs (148). At the end point, HAM-D and Montgomery-Asberg change from baseline were not significantly different between the placebo and pindolol arms of the study (12.5% change in both) (148).

Berman et al. completed a nine-week, 43-patient, double-blind, placebo-controlled trial in which patients were concurrently treated with fluoxetine and either placebo or pindolol for six weeks (149). From week 6 to week 9, all patients received fluoxetine and placebo (149). After two weeks, the rate of partial remission was 3% greater in the placebo group (149). At the time of completion of the study, 65% of the patients demonstrated at least partial remission without any significant difference between the groups (149).

Limitations of pindolol are the lack of replicated data, as well as adverse effects such as hypotension and exacerbation of asthma symptoms. This strategy may be useful for reducing time to antidepressant response, but more supportive data is warranted because the current evidence base is controversial.

Modafinil

Modafinil is a novel stimulant medication that is FDA approved for the treatment of narcolepsy, obstructive sleep apnea syndrome, and shift-work sleep disorder, and is often used for fatigue associated with multiple sclerosis. A putative minor mechanism of action is thought to be mildly increasing the level of dopamine by inhibiting its reuptake, because this drug needs an intact dopamine system to function. It has no other pharmacodynamic similarities to typical stimulants (100). It may also enhance histamine release from the tuberomammillary nucleus into the frontal cortex in a system that parallels the reticular activating system where true stimulants work. The net effect may be the enhancement of cognitive arousal, alertness, and concentration (100). It has, therefore, been called a "histamine alerter." In addition, modafinil may decrease GABA transmission (150). Modafinil is well tolerated with minimal abuse potential. It is metabolized by the P450 system and may cause a modest induction of the CYP3A4 system. Our group has found modafinil to be quite helpful in the treatment of fatigue associated with depression or fatigue associated with the use of other psychotropic medications or other comorbid illnesses. Schwartz et al. have completed small uncontrolled studies in this area (151–153). It is generally administered after initiation of antidepressant therapy with a dose range of approximately 50 to 400 mg/day, administered once daily in the morning.

DeBattista et al. completed a study in which 136 patients with a partial response to six-week antidepressant therapy were enrolled in a six-week, randomized, double-blind, placebo-controlled, parallel-group study (154). Patients received once-daily modafinil (100–400 mg/day) or matching placebo as an adjunct to antidepressant therapy. Modafinil rapidly improved fatigue and daytime wakefulness from weeks 2 through 6 versus placebo; however, there were no statistically significant differences after the sixth week (154). Augmentation effects of modafinil were not significant (154). Modafinil was well

tolerated when administered in combination with a variety of antidepressants (154). This data suggests that modafinil is an early response–facilitating agent, which has been replicated by Ninan et al. (155).

Menza et al. described a retrospective case series of seven patients with depression treated with modafinil to augment a partial or nonresponse to antidepressants (156). At doses of 100 to 200 mg/day, all the seven patients achieved full or partial remission within one to two weeks, with five to seven patients achieving a 50% decrease in HAM-D scores (156). All patients had residual tiredness or fatigue that was particularly responsive to augmentation (156).

DeBattista et al. completed a four-week, prospective, open-label study of 33 patients with major depression and partial responses to antidepressant therapy. These patients received an antidepressant plus modafinil titrated from 100 to 400 mg/day by week 4 (157). Changes from baseline to two weeks were significant [$p < 0.001$ for Beck depression inventory (BDI) and HAM-D], while changes from two to four weeks were not ($p = 0.69$ and $p = 0.441$) (157). The study suggested that modafinil is effective in facilitating antidepressant response and could also address fatigue, effort, and overall depression level (157). Mean CGI changes were similar, with improvements attributed to the changes in the first two weeks (157). On the neurocognitive battery, the Stroop interference test showed significant differences between weeks 1 and 4. No significant adverse events were noted (157). The Eppworth sleepiness scale and fatigue severity scale showed consistent statistical improvement when sleep and fatigue were specifically studied.

Modafinil appears to have beneficial effects, especially regarding fatigue-like symptoms. It is generally well tolerated, with doses in the range of 100 to 400 mg/day. Further studies are needed to ascertain effects on other core depressive symptoms, as well as long-term efficacy, safety, and tolerability.

Steroid Hormones

Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis has been implicated in the pathophysiology of depression. Depression associated with thyroid abnormalities and the depressogenic effects of progesterone (i.e., oral contraceptives) (158) and other steroids support a link between the endocrine system and affective disorders.

Estrogen

The use of estrogens in females for the treatment of postmenopausal depression has also been reported to be effective (159,160). The use of estrogens for the treatment of depressed women is also of theoretical interest in that there is evidence for increased monoamine oxidase activity in premenopausal depressed women, and estrogen (Premarin 0.125 mg/day) normalizes this activity as well as the depressed mood (161,162). These results suggest that a decrease in estrogen level may increase the metabolism of monoamines (a lowering of serotonin, norepinephrine, or dopamine, which may ultimately cause receptor upregulation). It is further suggested that the combination of antidepressants to increase available monoamines, when combined with estrogen, which decreases monoamine oxidase activity, may be an effective treatment for depressed female patients of premenopausal or menopausal age (163).

There are mixed reports in the literature on the use of estrogen for depressed women, in varying phases of their reproductive life cycle. The idea of using estrogen for depression was first introduced on the basis of the observations that estrogen levels decrease during menopause and fluctuations are seen in other periods of the reproductive cycle. Some models suggest that estrogen may modulate serotonin, catecholamines, and even cortisol activity, all implicated to play a role in depression (15,161,162,164–166).

While it is possible, from examination of current data, that the onset of major depression is increased after the menopause, there is little evidence that estrogen alone is effective in the treatment of depression in postmenopausal women (9). Four significant studies have found no improvement of depression in response to treatment with estrogen as a monotherapy (167–171).

There is evidence that estrogen might be effective as an augmentation to the treatment of depression in postmenopausal women and in postmenopausal women resistant to TCAs or SSRIs (166,167).

Schneider et al. pooled 127 women over 60 years old who were treated with sertraline with and without estrogen replacement therapy and reported on two 12-week, randomized, double-blind, multicenter trials for treatment of major depression (172). At end point, sertraline-treated women taking estrogen had significantly greater global improvement (79% vs. 58%) and better quality of life than those not receiving estrogen (mean $\pm$ SD: 73.5 $\pm$ 13 vs. 68.2 $\pm$ 14) (172). There was no reported difference in side effects between the estrogen and nonestrogen groups (172).

Clinicians should consider the potential risks and benefits of using estrogen replacement in peri- and postmenopausal females (e.g., personal/family history of breast cancer), especially in women who have residual symptoms or exacerbation of symptoms.

Testosterone

There is very little data on the use of testosterone as an augmenting agent in the treatment of depression. Testosterone is used to enhance libido in both men and women. In hypogonadal men, testosterone may improve mood and energy. In general, testosterone alone as an antidepressant has shown inconclusive results.

Nineteen subjects completed an eight-week, randomized, placebo-controlled study in which Pope et al. administered either transdermal testosterone gel or placebo to men with refractory depression and low or normal testosterone levels (173). Each subject continued his existing antidepressant regimen. Efficacy analysis revealed that the testosterone-treated patients had a significantly greater rate of decrease in scores on both the HAM-D and CGI than the placebo-treated patients (173). One report demonstrated onset of paranoia and aggression when methyltestosterone was added to augment imipramine (174).

Further studies are needed to ascertain the potential role of the use of testosterone as an augmentation for depression in males with normal and low testosterone levels. In patients with low baseline levels of testosterone, it is important to assess for potential comorbid illness and iatrogenic causes prior to initiating treatment. Baseline and follow-up serum testosterone levels are suggested; also consider the potential risks including irritability, aggression, prostate enlargement, and hepatic effects.

Cortisol Blockers

A developing antidepressant strategy directly targets the HPA axis. Abnormalities of the HPA axis were among the first and most consistently identified findings in depressed subjects. Such findings include elevated CSF corticotrophin-releasing hormone (CRH) levels, elevated cortisol levels, and diminished sensitivity to dexamethasone suppression. In preclinical and clinical studies, chronic antidepressant treatment normalized these findings. Therefore, agents that directly reduce the hypercortisolemia in depressed subjects were tested for antidepressant activity (15,175).

Two open trial studies (Murphy and Wolkowitz, 1993) have evaluated steroid-suppressant therapy (including metyrapone, ketoconazole, and aminoglutethimide) in treatment-refractory patients. Results are promising but preliminary, with the need for more data (175).

There is one randomized, controlled study in the literature evaluating the effect of metyrapone or placebo plus SSRI in 63 patients. Primary outcome criteria were the number of responders and the time of onset to action. Patients were evaluated at baseline, three weeks and five weeks with the HAM-D-17. Results showed a statistically significant higher proportion of patients receiving metyrapone had a positive treatment response at days 21 and 35 compared with placebo patients. While this study supports the use of metyrapone as an accelerant to the onset of antidepressant action when added to an SSRI, further study on long-term efficacy is warranted (176).

S-Adenosyl-L-Methionine

SAMe is an endogenous substance in mammalian tissue that shows potential mood-elevating effects in humans (177). Available for use in Europe, SAMe has medicinal usefulness in several disorders, particularly osteoarthritis (178). The first mood-elevating effects of SAMe were discovered serendipitously in the 1970s, when the substance was being investigated for use in the treatment of schizophrenia and was found to have mood-elevating properties (179,180). Several open-label and single-blind trials suggest antidepressant effects of SAMe on using intravenous or intramuscular (IM) routes of administration (180,181). Several double-blind trials reported that SAMe has equal or more effective antidepressant effects when compared with amitriptyline, imipramine, and clomipramine (182–184). In general, these studies show a trend toward a more rapid onset of action and less, if any, side effects with the use of SAMe. Precipitation of mania/hypomania has been reported with the use of SAMe as well (185). Its mechanism of antidepressant action remains unknown, however, the substance is an endogenous methyl donor for several CNS system neurotransmitters, including serotonin, norepinephrine, and dopamine, all of which are implicated in the pathophysiology of depression (180). This pathway also parallels and is utilized similar to L-methylfolate discussed earlier and may promote extra monoamine synthesis. SAMe also affects the lipid composition of cell membranes, which may also be involved in the pathophysiology of affective disorders (186). SAMe increases folate activity, which when deficient may also be involved in the pathogenesis of depressive disorders (187). All of the abovementioned studies are based on the use of IM or intravenous routes of administration. The reason for the preference of this route of administration over the oral route is based on limited investigation of the pharmacokinetics of SAMe,

suggesting that it has an unstable oral bioavailability. However, a recent open-label study using oral SAMe suggests antidepressant efficacy (179). Further investigation into its oral bioavailability as well as further controlled studies regarding its use in oral form are now proceeding. The evidence thus far suggests that SAMe is a novel antidepressant agent.

Berlanga et al. completed a 63-patient, eight-week, double-blind clinical trial in 1992 to evaluate the efficacy of SAMe in accelerating the onset of action of imipramine. Forty placebo nonresponders were given either dissolved SAMe IM or dissolved placebo IM with peroral imipramine 150 mg/day (188). Depressive symptoms decreased earlier with SAMe-imipramine than with placebo, but this difference was only significant through the second week (188). No adverse effects were noted in either the SAMe or the placebo group (188).

Atomoxetine

Atomoxetine was initially studied as a monotherapy for MDD in the 1980s. Unfortunately, doses were low (20 mg/day), which may have limited favorable efficacy outcomes in these early exploratory studies. Further studies with atomoxetine for MDDs in the 1980s were discontinued with the advent and enthusiasm of the SSRIs. However, interest in the role of norepinephrine in patients failing to adequately respond to an SSRI reemerged with the approval/availability of atomoxetine for ADHD.

While there may be a clinical interest in using atomoxetine as an augmentation for MDDs, there is a paucity of data in the literature. One controlled study (189) reported on the use of atomoxetine as an augmentation in TRD patients showing an inadequate response to a trial of sertraline. The outcome failed to demonstrate statistically significant differences between atomoxetine and had placebo when used as an augmentation for treatment failure to sertraline. However, this may have been a population of patients with more advanced TRD and limitations of maximal doses of atomoxetine doses used. Because our group has found atomoxetine useful as an augmentation with partial response to SNRIs, SSRIs, and other antidepressants, and we use a similar dosing strategy used in the Michelson study (189), it is worth reporting on this study's methods and outcomes. The study looked at TRD in 276 adult patients prospectively treated with sertraline (up to 200 mg—mean dose 161 mg/day) for eight weeks. Patients with no response or partial response (n=146) were randomized to atomoxetine augmentation (40–120 mg/day) or placebo for an additional eight weeks. Completion rates were similar between the two groups, and there were no differences in discontinuation rates for side effects. There was no difference between groups in the mean change in HAM-D, or in remission rates (40.3% atomoxetine/sertraline, 37.8% placebo/sertraline).

Papakostas et al. evaluated the efficacy and safety of atomoxetine as an adjunctive medication for residual fatigue in a naturalistic treatment setting (190). A retrospective chart review was conducted to identify MDD patients who had experienced significant symptom reduction (either partial response or remission) following treatment with antidepressants but who were continuing to complain of fatigue. Fourteen such patients with a HAM-D-17 item score of less than 11 where included. Twelve (85.7%) patients (nine remitters, three partial responders) received at least four weeks of atomoxetine treatment. The remaining two patients discontinued atomoxetine early secondary to increased

anxiety. There was a significant improvement in the brief fatigue inventory, and all the 12 patients were remitters at follow-up. Adverse effects included insomnia, increased anxiety, nausea, and dry mouth. Although preliminary, the authors suggest a possible augmentation role for atomoxetine for residual fatigue in MDDs.

Our group uses atomoxetine to augment partial response to SNRIs, SSRIs, mirtazapine, and bupropion—also, in patients with MDD and comorbid ADHD—starting dose at approximately 40 mg/day, slowly increasing to 80 to 120 mg/day. If results are not seen at these doses, we will consider increasing up to 160 mg/day. Adverse effects include anxiety, activation, somnolence, dry mouth, and urinary hesitancy/retention, and reports of cycle induction have been described (191). Blood pressure should be monitored, especially if multiple noradrenergic agents are being combined.

Other Augmentation Strategies

Other augmentation strategies reported in the literature include omega fatty acids, buprenorphine, ketamine, riluzole, tramadol, dopamine agonists, anticonvulsants, VNS, TMS, electroconvulsant therapy, and empirically based psychotherapies. These strategies are described in more detail in other chapters (192–204).

ANTIDEPRESSANT COMBINATIONS

Mirtazapine

Mirtazapine is a novel antidepressant with a proposed antidepressant mechanism that involves blockade of α-2 heteroreceptors. The result is norepinephrine and possibly dopamine release increases, combined with unique actions on several serotonin sub-receptors and histamine blockade (205). Mirtazapine ultimately seems to have mixed agonism and antagonism at the $5HT_{1A}$ receptor, as well as blockade at the $5HT_{2C}$ and $5HT_3$ receptors (100).

Carpenter et al. completed a 26-subject, four-week, double-blind, placebo-controlled combination study where mirtazapine (15–30 mg at bedtime) was added to current antidepressant medication (secondary to treatment failure) for the treatment of MDD (206). Primary antidepressants included venlafaxine, bupropion, and SSRIs at reasonable therapeutic doses and were taken for an average of 19 weeks. Forty-four percent of the subjects had clinical response to mirtazapine, demonstrating statistical significance (206). There was no difference in side effects between the groups in this short four-week study.

Carpenter et al. completed an open-label study of 20 patients who had failed four weeks of standard antidepressant treatment and were then subjected to four weeks of mirtazapine (15–30 mg) augmentation (207). At the four-week follow-up, 55% were responders, 30% were nonresponders, and 15% had discontinued, owing to weight gain and sedation (207).

The fourth level of the STAR*D study included patients who were either intolerant or failed to show an adequate response at the previous three levels of treatment (Fig. 1). Patients were randomly assigned to open-label treatment with either tranylcypromine (n=58) or venlafaxine ER plus mirtazapine (n=51) for 12-weeks (208). Tranylcypromine was dosed at 10 mg/day for two weeks and then increased weekly by 10 mg/day to a maximum of 60 mg/day. The mean dose of tranylcypromine at the end of treatment was 36.9 mg/day. In the

combination group, mirtazapine was given at 15 mg/day (weeks 1–3), 30 mg/day (weeks 4–8), and 45 mg/day (weeks 9–12); and venlafaxine ER was given at 37.5 mg/day (week 1), 75 mg/day (week 2), 150 mg/day (weeks 3–5), 225 mg/day (weeks 6–8), and 300 mg/day (weeks 9–12). At the end of treatment, the mean mirtazapine dose was 36 mg/day and the mean venlafaxine ER dose was 210 mg/day. There were no statistically significant differences between the two groups for rates of remission. Remission rates for the mirtazapine/venlafaxine ER groups were 13.7% (based on HAM-D) and 15.7% (based on QIDS-SR); and for tranylcypromine, 6.9% (based on HAM-D) and 13.7% (based on QIDS-SR). There was no statistically significant difference in remission rates between the groups; however, the reported side effects and attrition rate were lower with the combination group compared with tranylcypromine. Extrapolation of this data to clinical practice is limited by several factors including the slow titration of all medications, the low dose of tranylcypromine used in this design (and reported at end point), sample bias in each group regarding differences in history of medication intolerance . Also, 71% of the tranylcypromine patients received only two weeks of treatment, and only 15% of the original level 1 nonresponders elected to enter level 4 of the study (Fig. 1) (208).

Because it is novel in its pharmacological action and can reduce depressive and anxious symptoms, as well as adverse effects from the use of other antidepressants, our group has found mirtazapine to be of particular benefit. Mirtazapine can help decrease insomnia symptoms, sexual dysfunction, and gastrointestinal (GI) upset associated with SSRIs and SNRIs. The potent $5HT_3$ blockade can reduce nausea associated with acute SSRI treatment. Potential appetite increase secondary to antihistamine properties as well as potential sedation can be limitations, whereas they may be beneficial for residual poor appetite or insomnia or when nausea may accompany depression. Given the $5HT_3$ antagonism of this compound, however, higher doses may be associated with less sedation in some patients.

Bupropion

Bupropion is an effective antidepressant medication whose FDA approval predates the SSRI fluoxetine. The antidepressant mechanism of bupropion still remains speculative, although evidence suggests that it increases the neurotransmission of norepinephrine and dopamine activity. It is among the few available antidepressant medications without direct effects on increasing 5HT activity. With this stated, many clinicians believe that the combination of bupropion plus a serotonergic agent can be quite successful not only in terms of efficacy but also in reducing prominent adverse effects such as sexual dysfunction, weight gain, and fatigue.

Early open-label studies suggested the efficacy of bupropion when used in combination with other antidepressants. DeBattista et al. conducted a six-week prospective, open-label trial of 28 patients to establish the efficacy of bupropion combined with an SSRI or venlafaxine in partial responders and nonresponders (209). At week 6, HAM-D and BDI scores were significantly reduced when compared with that at baseline (39% and 44%, respectively) (209). Sixty-four percent of the patients had ratings corresponding to that of the "much improved" or "very much improved" state by week 6 on the clinician-rated CGI (209). Headache and insomnia were the most commonly reported adverse

effects, with incidence of 56% and 44%, respectively. One patient discontinued the study owing to the side effect of increased anxiety (209).

Lam et al. conducted a six-week, naturalistic, open-label cohort study of 61 patients comparing the effects of combining citalopram and bupropion sustained release versus switching to the other monotherapy in treatment-resistant depression (210). The combination option showed superiority to the monotherapy switch in the structured interview guide for the HAM-D-17, the seasonal affective disorders version change score (–14.8 vs. –10.1), and the proportion of patients in clinical remission (28% vs. 7%) (210). There were no differences in the proportion of patients who had side effects or in the severity of the side effects experienced.

Bodkin et al. conducted a chart review of 27 patients treated with the combination of an SSRI and bupropion (211). These patients were first observed in treatment with either SSRI or bupropion alone and were found to be partial responders. The second agent was added to the first for a mean time of 11.1 months (211). Ultimately, greater symptomatic improvement was found in 70% of the 27 subjects within the first 11 $\pm$ 14 months of combined daily use of bupropion (243 $\pm$ 99 mg) with SSRI (31 $\pm$ 16 mg fluoxetine equivalents) than with either agent alone (211). Adverse-effect risks were similar to those of monotherapy (211).

Spier treated 25 consecutive patients with bupropion in combination with an SSRI or venlafaxine after monotherapy failure or venlafaxine-induced side effect development (212). Fifty-six percent of the patients responded to combination therapy based on CGI score changes at an average follow-up time of 21.3 months (212). Eighty percent of subjects receiving combination therapy responded, while only 20% responded when the combination was given to treat monotherapy-induced side effects (212). Combination therapy was generally well tolerated, with headache, nausea, diaphoresis, and decreased concentration being limited to only three cases (212).

Data from STAR*D provided information on the second level of treatment (Fig. 1) on the use of buspirone augmentation compared with bupropion SR combination treatment or CBT augmentation to citalopram after a patient fails to adequately respond/remit to monotherapy with citalopram. This was the first level of switch/augmentation/combination offered to any patient who either showed inadequate response/remission or was unable to tolerate a 14-week trial of citalopram during level 1 (Fig. 1). Two hundred and eighty-six patients were randomized to buspirone augmentation (maximum dose 60 mg/day in divided doses), 279 patients were randomized to bupropion SR combination (maximum dose 400 mg/day in divided doses), and 85 patients were randomized to CBT augmentation (3,4). All three groups showed similar (not statistically significant difference) remission rates based on QIDS-SR criteria; 26.9% (buspirone plus citalopram), 31.8% (bupropion SR plus citalopram), and 29.4% (CBT plus citalopram) (3,4). There were higher dropout rates for the buspirone augmentation group (20.6%) compared with bupropion SR combination (12.5%) and CBT augmentation (10.5%) (3,4). Of interest, the frequency of concomitant anxiolytic and hypnotic medication was similar between the two medication augmentation/combination groups.

Tricyclic Antidepressants/Monoamine Oxidase Inhibitors

The combined use of TCAs and MAOIs has been suggested for years as an alternative treatment for persons with resistant depression. Theoretically, the

rationale of using both the antidepressant agents would be to combine the effect of the TCA-mediated neurotransmitter reuptake inhibition with enzyme inhibition of the MAOI and thus bring about an increased amount of neurotransmission at the postsynaptic receptor for all three major amines involved in the pathogenesis of depression. However, the combined use of a TCA and an MAOI is warned against in the Physician's Desk Reference (213) on the basis of the possibility of the occurrence of hypertensive and hyperthermic episodes reported with such combinations. It is recommended to wait for 10 days before starting a TCA after discontinuation of an MAOI or before starting an MAOI after discontinuation of a TCA (213). However, there are several reports of safely switching from a TCA to an MAOI within a four-day period and of this drug combination being used safely (214–217). In fact, there is evidence to suggest that certain TCAs, particularly amitriptyline, may help protect against tyramine-induced hypertensive reactions seen with MAOIs (114); however, such a drug combination should not keep the patient from adhering to a low-tyramine diet.

Early evidence of TCA/MAOI efficacy in treatment-resistant depression is derived from anecdotal reports and uncontrolled studies. Although not performed under controlled conditions, there are reports of depressed persons who failed to respond to monotherapy with TCAs or MAOIs or who failed to sustain improvement with ECT responding to TCA/MAOI combinations (215,218,219).

Several controlled trials report that the TCA/MAOI treatment combination is not superior to either treatment alone (220,221). However, even these trials do not adequately study treatment-resistant depression specifically.

While the actual efficacy of the TCA/MAOI combination for treatment-resistant patients remains to be demonstrated in controlled studies, this treatment should be utilized only when the patients fail other conventional treatments. The TCAs recommended for use are the more serotonergic agents amitriptyline, trimipramine, and doxepin (222). Although tranylcypromine is noted for increased risk of hypertensive reactions, it is reported to be safe when used in combination with TCAs, as are phenelzine and isocarboxazid (217,220). It is generally not recommended to use imipramine, desipramine, nortriptyline, or clomipramine, all of which possess at least some noradrenergic properties. On the basis of reports on the safety of TCA/MAOI combination, it can be started simultaneously, or the TCA can be started first and then treatment with the MAOI can be initiated. The use of lower doses—lower than when either drug was used alone—is recommended when initiating such a combination.

Heterocyclic Antidepressants/Selective Serotonin Reuptake Inhibitors

SSRIs have claimed the status as first-line treatment for depression since the 1980s, however, some patients do not fully remit and require further pharmacological action beyond serotonin. In the early years of the use of SSRIs, clinicians remained familiar with the use of TCAs/heterocyclics (HCAs) and commonly "overlapped" or combined treatments to achieve a "broader" pharmacological effect. Animal models and controlled/open-label reports suggested possible rapidity of response and perhaps a more robust response with combination compared with that achieved with monotherapy. HCAs are metabolized via the CYP2D6 pathway and therefore necessitate caution when being combined with other "2D6" drugs such as SSRIs/SNRIs (fluoxetine, paroxetine,

duloxetine, etc.). As with other TCAs, drug levels can be obtained five to seven days after the dosage is initiated and 8 to 12 hours after the last dose.

In an open, four-week, non-controlled trial completed in 1991 by Nelson et al., 14 inpatients with major depression were administered both desipramine and fluoxetine, and their responses were retrospectively compared with those of 52 inpatients who were previously treated with desipramine alone (223). At weeks 1, 2, and 4 of the study, the response to the desipramine-plus-fluoxetine combination was better than that obtained when desipramine was given alone (week 1, 42% vs. 20%; week 2, 62% vs. 30%; week 4, 71% vs. 0%; complete remission defined as a change in HAM-D score >75%) (223). Hypotension, tachycardia, and allergic rash were noted as consequences of inappropriate TCA dose and imprecise monitoring of plasma drug levels (223).

Weilburg et al. (224) report the effects of fluoxetine added to the treatment of 30 depressed outpatients who showed a poor response to an adequate trial of an HCA. Improvement was seen in 86.7% of the patients. In all of the cases reported, the dose of the HCA was lowered after fluoxetine was added, with an average HCA maintenance dose (in imipramine equivalences) of 70.6 mg/day. Fluoxetine dose ranged from 20 to 60 mg/day. The HCA was discontinued for 12 of the 26 responders, of whom eight relapsed but recovered when the HCA was restarted. The HCAs used included amitriptyline, desipramine, doxepin, imipramine, maprotiline, nortriptyline, trazodone, and trimipramine. No adverse events were reported.

Levitt et al. completed an eight-week, non-controlled study in which 13 patients with major depression, who had failed treatment with desipramine or imipramine and were currently unsuccessfully being treated with fluoxetine, were given desipramine or imipramine along with their dose of fluoxetine (225). Of the 13 subjects, 54% had greater than 40% decrease in HAM-D scores and 31% of this group had greater than 50% decrease in HAM-D (225). At week 3, responders had a higher mean TCA level when compared with nonresponders (225). No adverse events were reported.

Seth et al. examined eight cases of treatment-resistant depression treated with a combination of nortriptyline and a new SSRI, with or without concurrent lithium therapy (226). Notable improvement was seen in all patients in whom other drug regimes, such as MAOIs, TCAs, neuroleptics, and ECT, had been ineffective (226). There were no reported significant side effects among the eight cases, seven of which were elderly patients (226). In each case, combination treatment was more effective than single treatment modalities.

Zajecka et al. reported on 25 nonresponders to at least four weeks of open-label fluoxetine treatment. An HCA was added to fluoxetine, with dosages then titrated up (227). A retrospective analysis demonstrated that 35% of subjects who demonstrated a partial response to fluoxetine responded fully when an HCA was added to fluoxetine (227). Five of the responders (71%) who had previously failed with monotherapy with HCA responded when HCA was used with fluoxetine. Five subjects who demonstrated significant improvement with fluoxetine but had mild residual depression symptoms experienced a partial improvement with the addition of HCA (42.7% HAM-D change) (227). One nonresponder subject experienced a generalized seizure with fluoxetine and maprotiline, which were then discontinued without significant sequelae (227).

Maes et al. completed a five-week, double-blind, placebo-controlled study of 26 patients with treatment-resistant depression (228). After one week of

trazodone treatment, patients were randomized to receive placebo, pindolol, or fluoxetine in addition to the trazodone for four weeks (228). With the outcome measure being a 50% reduction in HDRS, 72.5% of patients treated with trazodone plus pindolol, 75% of patients treated with trazodone plus fluoxetine, and 20% treated with trazodone plus placebo showed a clinically significant response (228). No unique adverse events were noted (228).

Dual Serotonin-2 Antagonists and Reuptake Inhibitors (Trazodone, Nefazodone)

Nefazodone and trazodone are novel agents with dual serotonin-2 antagonism and reuptake inhibition. Both act by potent blockade at the $5HT_{2A}$ and weak serotonin reuptake inhibition. Nefazodone also has weak norepinephrine reuptake inhibition as well as weak α-1-adrenergic-blocking properties. Trazodone also contains α-1-antagonist properties but lacks the norepinephrine reuptake inhibition capability of nefazodone (100). In many patients, trazodone produces sedation that can be poorly tolerated at therapeutic doses. It is for this reason that many clinicians choose to combine this drug in low doses (25–150 mg at bedtime) with other antidepressants, as an off-label hypnotic. Trazodone can improve overall sleep and thus theoretically reduce depressive symptoms associated with insomnia. In addition, the $5HT_2$ antagonism may produce anxiolytic effects as well as potential sexual dysfunction reversal associated with SSRIs. Apart from marked sedation, priapism is a side effect that the patient should be made aware of, and informed consent must be obtained from the patient before initiating treatment with trazodone.

Nefazodone is a unique antidepressant, but recent reports regarding its use are rare. Potential liver damage has resulted in a decline in its use in the United States. As seen in the case of trazodone, nefazodone's receptor profile with $5HT_{2A}$ blockade can be quite helpful in reducing adverse effects such as sleep and sexual dysfunction associated with the use of SSRIs. If $5HT_2$ blockade is desired, safer alternatives may include the use of mirtazapine or second-generation antipsychotics in low to moderate doses. In addition, the lack of antihistamine activity reduces the likelihood of sedation and increases the tolerability profile.

Taylor and Prather completed a non-placebo-controlled, nonrandomized cohort study of 11 patients with treatment-resistant depression and/or comorbid anxiety disorders who were given increasing dosages of nefazodone in addition to their previous regimen until an optimum response was achieved (229). After augmentation, 63% achieved complete remission of depressive symptoms (229). In each of the 11 cases, nefazodone was efficacious and well tolerated in the treatment of depression and anxiety (229).

Our group tends to dose this drug once daily at bedtime, as opposed to twice daily, mainly for compliance and to reduce the relatively small likelihood of sedation during the day. This drug may also improve sleep and normalize sleep architecture in this augmenting strategy.

CONCLUSION

This chapter started with a basic clinical introduction regarding the pros and cons of polypharmacy in MDD. We have now completed a thorough review of the evidence base that is used to support this common practice. Polypharmacy may be the rule rather than the exception (230) when a clinician attempts to help

a patient reach full remission of MDD symptoms and is gaining popularity when side effects need to be alleviated for the patient to remain adherent to long-term medication management. Finally, as you have noticed, the evidence base is somewhat lacking when compared with monotherapy data. Clinicians should always take each individual case into account and weigh the risks/benefits accordingly. The key to successful rational polypharmacy is to understand how each medication facilitates certain transmitter pathways and to attempt to match up residual symptoms with these malfunctioning pathways especially when definitive data is lacking.

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4 Adherence, Compliance, and Discontinuation in Depression

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INTRODUCTION

Antidepressants are the most commonly prescribed medicine accounting for about 120 million prescriptions per year, or 5% of all drugs prescribed in the United States, according to Centers for Disease Control and Prevention (1). In accordance with national recommendations, they are often prescribed for periods of 6 or 12 months. In clinical practice, they may be continued for decades. Only recently has it become clear that most people have great difficulty following an extended course and, as such, are often labeled "nonadherent" (2,3,14). However, this is an oversimplification of a complex problem that includes discontinuation, missed doses, excess doses, and in some cases, recommencement after prematurely stopping. As depression is increasingly thought of as a chronic illness, it is useful to compare medication habits with other long-term conditions (4). Barber and colleagues found that only 16% of patients taking medication for stroke, coronary heart disease, asthma, diabetes, and rheumatoid arthritis were adherent, problem free, and in receipt of sufficient information when examined at 10 days (5). The following chapter comprises a thorough literature review with regard to treatment noncompliance in major depressive disorder.

New Nosology of Compliance Problems

An understanding of why patients have difficulty taking medication as prescribed has advanced recently with improved terminology for types of nonadherence (Fig. 1). Whereas we previously talked simplistically of compliant versus noncompliant, it is now recognized that there is a continuum of difficulty following medication advice. This continuum can be represented by the concepts of full and partial nonadherence as well as intentional and unintentional nonadherence. A small proportion (10–20% in the case of antidepressants) of those prescribed a new drug will not collect the prescription and/or commence treatment. This is usually a reflection of an individual's uncertainty about the benefits versus hazards about that drug. Of those that do start, some take medication to excess, but the most common error is that occasional doses are omitted. This is called partial adherence and is extremely common, certainly more common that full discontinuation. Not infrequently patients miss doses intentionally because of inconvenience and also because of the belief that medication can be taken largely "as required." Doctors are not good at convincing patients to take medication for relapse prevention after the patient begins to feel better. Most of those taking medication for a long term, particularly those receiving little follow-up care, will stop taking the medication

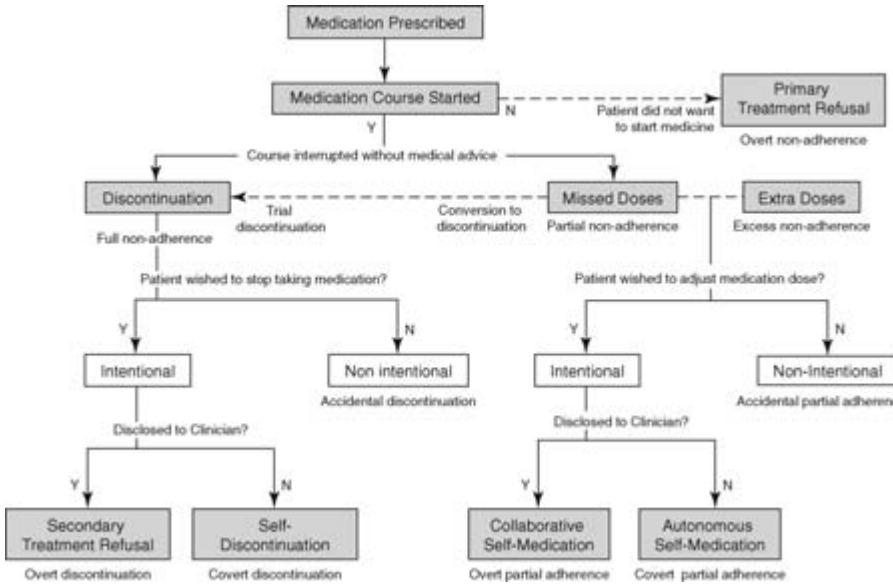

FIGURE 1 A new nosology of medication adherence.

themselves. They may or may not inform their doctor. Many will initially experiment with a period without medicine (trial discontinuation), after which they will either restart or decide to discontinue completely. Many of these decisions are entirely rational, given the information available to the patient at that time (6). However, insight does play a role. Put another way, if someone does not perceive himself or herself as ill and is afraid of adverse effects, he or she is unlikely to put much effort into starting and continuing with a course of medication.

The aim of this review was to examine the causes and consequences of antidepressant adherence using the following headings: (*i*) epidemiology of antidepressant adherence, (*ii*) consequences of antidepressant nonadherence, (*iii*) understanding discontinuation with antidepressants, and (*iv*) measures to reduce antidepressant nonadherence.

METHODS

A systematic literature search and critical appraisal of the collected studies was conducted. The following abstract databases were searched. Medline 1966—December 2008, PsycINFO 1887—December 2008, Embase 1980—December 2008. In these databases the keywords "depression or depressive or mood or affective" and "antidepressant" and "adherence or compliance or discontinuation or stop" were used. In the following full text collections including Science Direct, Ingenta Select, Ovid Full text, and Wiley Interscience the same search terms were used but as a full text search and citation search. The abstract database Web of Knowledge (7.10, ISI) was searched, using the above terms as a text word search, and using key papers in a reverse citation search.

RESULTS

Epidemiology of Antidepressant Adherence

Several large-scale studies suggest that adherence difficulties are common for patients who suffer depression (see Box 1 for definitions). Tierney and colleagues found that of 240,604 patients who were given a new antidepressant prescription, 70% discontinued within six months (7). Examining adherence data from over 740,000 newly initiated immediate-release selective serotonin reuptake inhibitor (SSRI) patients, Eaddy and associates found that nearly 50% of patients failed to adhere to therapy for 60 days or more, and only 28% were compliant at six months (8). Eaddy and colleagues examined 65,753 patients in a large managed care claims database who received SSRI prescriptions between June 2001 and December 2002 (9). Of these patients, 36% discontinued therapy within 90 days of initiating treatment; 23% were compliant but changed antidepressants; and 41% were compliant for 90 days, but of these 13% had partial adherence in the next 90-day period.

Types of Poor Medication Adherence

Full discontinuation
Stopping a prescribed course of medication against medical advice (or in the absence of medical advice)

Partial nonadherence
Interrupting a prescribed course of medication against medical advice (or in the absence of medical advice)

Optimal adherence
Taking the prescribed medication at the correct time and at the correct dose on a regular basis.

In the Medical Expenditure Panel Survey, Olfson and colleagues studied 829 people who had recently started antidepressant treatment for depression (10). Of them, 42% discontinued their antidepressants during the first 30 days and 72% had stopped within 90 days. Bambauer and colleagues documented partial nonadherence in 75% of depressed individuals, culminating in an average of 40% of days without dispensed antidepressants (11). In a prospective cohort study, in a large national database study, Cantrell et al. conducted a retrospective study of almost 23,000 patients recently prescribed SSRI therapy for depression or anxiety (12). Using several definitions, only 43% of patients were adherent to antidepressant therapy at six months. One-third of the poorly adherent patients attempted to restart antidepressants at least once during this period. In a retrospective, observational study of 4312 depressed patients, Akincigil et al. measured treatment adherence using pharmacy refill records during the first 16 weeks (acute phase, $n = 4312$) of treatment and then up to 33 weeks (continuation phase, $n = 2188$) (13). Measures were based on the Health Plan Employer Data and Information Set (HEDIS) for outpatient depression care. Of these patients, 50.7% were adherent in the acute phase, and of those, only 41.5% remained adherent in the continuation phase. Low follow-up from a psychiatrist, younger age, comorbid alcohol or other substance abuse, comorbid cardiovascular/metabolic conditions, use of older generation antidepressants, and residence in

lower-income neighborhoods were associated with lower acute phase adherence. Stein and colleagues examined antidepressant adherence in relation to anxiety disorders with or without depression (14). In a sample of 13,085, 57% were nonadherent to antidepressant therapy at six months. Nonadherence was defined by a medication possession ratio less than 80%. Patients who received specialist mental health were more likely to be adherent (48.5% vs. 40.7%), as were those with dual diagnoses of anxiety and depression (46.8%) (vs. anxiety alone, 40.2%).

These adherence rates represent real-world results as most have been collated from large health care databases. Further useful information comes from trial environments in which adherence is closely monitored and follow-up is extremely regular. Even here discontinuation rates for those taking SSRIs are above 70% (15). Several recent smaller studies on antidepressant adherence have also provided valuable data. Brook and colleagues in Amsterdam used six-month follow-up data of 147 primary care patients who were newly prescribed a non-TCA (16). Adherence behavior was closely monitored using an electronic pill container over a total of more than equivalent 20,000 days. The mean number of correct intakes was 74%, with 69% exhibiting adequate adherence (defined as taking more than 80% of medication doses). Remarkably only 3% of the patients followed the medication regimen exactly as prescribed. Hunot et al. conducted six-month prospective study of new antidepressant starters at five primary care practices in Southeast England (17). Of them, 9% did not start taking their medication. Of 147 completors, only 19% took antidepressants correctly throughout the six-month period; 50% discontinued, and of these, one-third later restarted. Bockting and colleagues prospectively followed 172 euthymic patients with recurrent depression prescribed antidepressants (18). Of them, 42% used antidepressant continuously, and only 26% of the patients used antidepressants as recommended by international guidelines. In a subsample followed for two years, 20.9% were continuously intermittently nonadherent and 30.8% continuously adherent, leaving 48.2% who had partial adherence (19). Nonadherence predicted time to recurrence. Cooper and colleagues used data from 634 individuals, taking psychotropics from the 2000 British Survey of National Psychiatric Morbidity. Of them, 34.2% reported incomplete adherence to their psychiatric medication (20). Reduced adherence was associated with SSRI and tricyclic antidepressant (TCA) use but not antipsychotics. This was one of the only studies to examine excess medication use. Of the people studied, 9.4% reported that they had sometimes taken more medication than prescribed, and in 81% of cases this was to achieve better symptom control. Other reasons included deliberate overdose (7%); feeling low, depressed, or stressed (8.2%); and catching up with a missed dose (3.5%).

ten Doesschate et al. (21) also studied 131 recurrently depressed patients who were assessed seven times for self-reported adherence over two years. Nonadherence ranged from 39.7% to 52.7% (mean 47%); 20.9% were always nonadherent and 48.4% were intermittently nonadherent. Only 30.8% were continuously adherent over two years.

One new finding is that of those who started SSRI treatment, about 22% collect only a single prescription. One-third of these do not start medication at all, and two-thirds quickly discontinue usually within days or weeks (22). Fear of adverse effects and the actual occurrence of adverse effects were main reasons for not accepting SSRI treatment. Of the non-accepters, 55% discontinued treatment without informing their general practitioners (GPs).

In conclusion, it is troubling that major depression is considered a treatable illness with a myriad of available safe, tolerable, and effective medication, but reasonable compliance with said treatment may actually represent a minority of cases. It also seems clear that as medication noncompliance increases, relapse in depression occurs.

Consequences of Antidepressant Nonadherence

There is considerable evidence that premature medication discontinuation can be costly (23,24). Undisclosed (covert) nonadherence appears to be particularly hazardous probably because alternatives are not explored. That said, in some cases nonadherence may be the sensible choice when current medication is causing more harm than benefit. Thus nonadherence may be costly, but this is not always the case. Unfortunately there have been very few studies exploring the consequences of poor and partial adherence to antidepressants or premature discontinuation of antidepressants in clinical settings.

Studies of relapse following planned discontinuation in trial environments illustrate high relapse rates, but these may not be comparable to true patient-led discontinuation. Recently, Akerblad et al. studied the consequence of non-adherence in 835 patients who were followed for two years (25). Response and remission rates were significantly higher in adherent compared with non-adherent patients. For example, 48.3% of adherent patients had a sustained response compared with 25.4% of nonadherent patients. However, there was little difference in relapse rates although the mean time from response to first sign of relapse was somewhat longer in the adherent patients (302 days vs. 249 days). Bockting et al. for the Delta study group found a 60.4% relapse rate over two years for those continuously taking the antidepressants compared with 63.6% in those who took medication intermittently (18). In patients who stopped taking antidepressants after remission but who received additional preventive cognitive therapy, the recurrence rates were significantly lower than in non-antidepressants-using patients treated with usual care (8% vs. 46%).

Understanding Discontinuation with Antidepressants

What factors can explain these high rates of discontinuation and even higher rates of missed medication? Slowly, evidence is emerging that in the vast majority of cases, preexisting treatment preferences, trust in medication/the prescriber, and treatment-emergent problems are more important than severity of depression or loss of insight. In fact most cases of discontinuation appear to be intentional and rational, given the information available to that individual. What does the research suggest about predictors of antidepressant nonadherence?

Confidence in Antidepressant Treatment

Sirey et al. found that perceptions of stigma about depression at the start of treatment predicted subsequent antidepressant adherence three months later (26,27). Surveys in many countries consistently report that more than three-quarters of people believe that antidepressants are addictive and most prefer psychological treatments or no treatment at all (28–31). In the IMPACT study of collaborative care for late-life depression, 38% reported that they would prefer

an antidepressant, 51% reported that they would prefer counseling or psychotherapy, and 4% reported that they would prefer "no treatment at all."[a] In this study previous experience with a treatment type was the strongest predictor of preference. In addition, medication preference was predicted by male gender and diagnosis of major depression (vs. dysthymia) (32). In a large primary care survey although 83% wanted active treatment for depression (33), only 27% preferred antidepressants, 29% preferred individual counseling, and 26% preferred group counseling. Factors associated with selecting counseling over medication were female gender, ethnicity (African-Americans compared with whites), greater knowledge about counseling, paid sick leave, and no recent antidepressant treatment. Col et al. (34) found that 50% of depressed patients believed they did not need their antidepressants when they began to feel better or could be taken "as required." A negative experience of prescribed medication has a negative influence on current adherence behavior (35). Brook et al. found that attitude toward antidepressants was the most important predictor in determining reliable adherence behavior (16). A favorable attitude to medication and increased confidence in managing side effects predicted antidepressant adherence in a primary care randomized controlled trial (RCT) (36). Aikens and coworkers went further and modeled the risk attributable to concerns about medication (37). Baseline skepticism about starting an antidepressant conferred a 62% increase in the risk of premature discontinuation over nine months. In a survey of 165 patients with major depression, Aikens and colleagues also recently demonstrated that skepticism about antidepressants is strongest among younger patients who have never taken antidepressants, view their symptoms as mild and transient, and feel unclear about the factors affecting their depression (38). Hunot et al. found that concerns about antidepressant side effects, general worry about taking antidepressants, and preference for different treatment predicted poor adherence (17). They calculated that a patient who has strong concerns about unpleasant side effects, is generally worried about taking antidepressants, and has a preference for or is uncertain about different treatment has a 16% probability of sustained antidepressant in the first month, decreasing to a 2% probability over six months.

Aikens and colleagues also found that patients' perceived necessity was associated with older age ($p < 0.001$), more severe symptoms ($p = 0.03$), longer anticipated duration of symptoms ($p = 0.001$), and attribution of symptoms to chemical imbalance ($p = 0.005$) (38). Perceived harmfulness was highest among patients who had not taken antidepressants before ($p = 0.02$), attributed their symptoms to random factors ($p = 0.04$), and had a subjectively unclear understanding of depression ($p = 0.003$). Neither belief was significantly associated with sex, education, age at first depressive episode, presence of melancholia or anxiety, psychiatric comorbidity, or clinical setting.

Effectiveness

In a large study of over 15,000 patients treated with fluoxetine in general practice, 33% stopped in the first six weeks (39). While 64% stopped after feeling better, 11% did so because of lack of response and 14% because of

[a] Of patients, 7% stated that they had "no preference."

tolerability issues. Among 210 patients previously treated for depression who stopped medication, Ashton and coworkers (2005) found that the most common reason for discontinuation was lack of efficacy (reported by 44%) (40). However, many patients stop antidepressants intentionally, when feeling better. In fact two studies found that a third of patients stop by three months, citing feeling better as the reason and 55% stop when feeling better by six months (41,42). Thus both successful and unsuccessful treatments often lead to patient-led discontinuation.

Adverse Effects

Adverse events are an important but avoidable (or at least reversible) reason for discontinuing treatment and not wanting to restart. Ayalon et al. (43) found that *intentional* nonadherence was associated with concerns about side effects of antidepressants as well as the associated stigma. In a survey of 344 antidepressant users, the most common reason for less-than-perfect compliance was side effects (40). The experience of one or more bothersome adverse effect means that an individual is three times more likely to stop medication (44). Such complications include weight gain (31%), inability to have erection (25%), difficulty reaching orgasm (24%), and fatigue (21%) (40). In a study of 406 inpatients and outpatients prescribed an SSRI, experiencing one or more *extremely* bothersome side effects was associated with more than a doubling of the risk of discontinuation, but the presence of side effects less severe than *extremely* bothersome was not significant (45).

Accidental Omissions

If one examines missed doses rather than full discontinuation, then "forgetting to take the tablet" is the most common explanation (46). This is encouraging as this allows scope for reminder systems (see below). In the 2000 British Survey of National Psychiatric Morbidity about a third of patients had self-reported adherence problems. Common explanations were forgetting, losing, running out (37.4%); thinking medication was unnecessary (24.6%); reluctance to take drugs (18.9%); and side effects (14.2%). Those giving forgetfulness as a reason were younger and were more often taking SSRIs. In the large Alberta Mental Health Telephone Survey from Calgary poor compliance was assessed in 5323 adults by the question "When you take antidepressants, are there any days when you took less than you were supposed to?"; 42% individuals missed medication, and 64.9% reported that forgetfulness was the most common reason for missed medication (47). Similarly Ashton et al. found that difficultly in remembering to take medication accounted for 43% of cases of poor compliance (40). Forgetting to take all doses is related to regimen complexity, cognitive impairment, and the duration of institutionalization, and ironically the presence of depression (48).

Choice of Antidepressant

One obvious factor that deserves further comment is the effect of the specific antidepressant drug. Each pharmaceutical company claims superiority of tolerability, but does this translate into differences in clinical practice? Surprisingly

robust differences in large-scale head-to-head studies are difficult to find. For example, work to date hints that discontinuation with tricyclics is only marginally worse than with newer antidepressants (49–53). Similarly, differences between SSRIs according to data from 14,933 patients on three brand name SSRIs (15) and a larger study on 116,090 patients newly initiated on SSRI in the IHCIS National Managed Care Database are marginal (54). Currently factors other than specific antidepressant choice seem to be the major determinants of partial nonadherence and premature discontinuation.

Regimen of Antidepressant

A meta-analysis of 22 studies found no difference in number of dropouts when an antidepressant was administered once a day or on multiple occasions and whether or not the antidepressant had a short half-life (12 hours) (55,56). Two studies found that patients receiving controlled-release paroxetine were 28% to 39% less likely to discontinue therapy during a 180-day period compared with those receiving immediate-release SSRIs (57,58). A recent database study of over 3000 patients found considerably better treatment adherence with once-daily versus twice-daily bupropion (59).

Measures to Reduce Antidepressant Nonadherence

Collaborative Care Interventions

There are numerous potential ways of improving adherence behavior from simple to complex (60). Large-scale studies in medical settings hint that a dramatic effect on adherence behavior is rare (61). In mental health settings authors have often examined a package of care, usually called "Collaborate Care." The collaboration is between mental health professionals and primary care practitioners. Key components may include patient education and support, monitoring of symptoms, psychological treatment option, and help with treatment adherence. Several reviews in depression show benefits of collaborate care upon medication adherence although individual differences between studies are large (62,63). Collaborative care packages have demonstrated a benefit in 14 of 28 studies that used adherence as an outcome (62). However, disentangling each key component to discover which specific aspects help may be difficult or impossible. For this, other study designs are needed. Collaborative care models, similar to diabetes management models, utilize many providers from different disciplines and utilize much collateral, non-billable time. Often a net result is improved compliance, care, and even outcomes but at the expense of increased cost.

Specific Interventions

Only a few specific strategies have been rigorously tested in depression (64–66). Katon and colleagues (67) conducted an RCT involving 386 patients with recurrent major depression or dysthymia who had largely recovered after eight weeks of antidepressant treatment. Patients were randomized to a relapse prevention program (receiving 2 primary care visits with a depression specialist and 3 telephone visits over a year) or usual primary care. Those in the intervention group had significantly greater adherence and significantly fewer

depressive symptoms, but not fewer episodes of relapse/recurrence over the 12-month follow-up period. Vergouwen and colleagues (68) reviewed six interventions conducted in mental health outpatients and 13 studies conducted in primary care. Of those in psychiatric settings, five tested education as an adherence-enhancing intervention, and three of these studies from Myers group at the University of Keele could not demonstrate any appreciable effect (69,70). However, Myers and Calvert (71) and Altamura and Mauri (72) both demonstrated significantly better adherence in patients who received verbal and/or written information about side effects of antidepressant medication. A recent review of simple strategies involving giving patients more information about their medication found 17 studies (73). Generally, adherence was 11% to 30% higher in the intervention groups than in the control group. A combination of oral and written information seemed to have an added value as compared with supplying exclusively oral or written information. However, no significant differences were seen for frequency of side effects, relapse or admission rates, symptoms and quality of life. Myers and Branthwaite (74) were the only group that tested the influence of the number of dosing complexity as well as the effectiveness of allowing patients to choose their own dosage regimen. Adherence was significantly better in only those patients who were allowed to choose.

From the 13 primary care studies reviewed by Vergouwen and colleagues, three tested educational interventions but two involved a leaflet alone. None were successful at improving adherence (75–77). The same group published a primary study. In an RCT, Vergouwen et al. (2005) compared a depression treatment package with simply following up patients using the same process and ensuring that evidence-based doses of medication were used. Thirty GPs were randomized, and 211 primary care patients with current major depression were included. They found no difference in adherence rates or depression outcome (78). Of note, adherence rates were above 68% in both arms at 26 weeks.

Since early 2003 a further eight studies have been published (62). The largest was a randomized study involving 1031 depressed patients that looked at an educational program and therapeutic drug monitoring in those treated with sertraline for 24 weeks in primary care (79). Here Akerblad and colleagues found that neither of the interventions resulted in a significant increase in adherence rate. However, significantly more patients in the education group responded at week 24 compared with patients in the control group. Two pharmacist-led psychoeducation programs have recently been published, although one was underpowered, with just 74 participants (80). However, Adler and colleagues conducted a robust RCT of a pharmacist intervention (telephone or face to face) for 533 patients with major depression and/or dysthymia. At six months antidepressant use rates for intervention patients exceeded controls (57.5 vs. 46.2%, $p = 0.03$) (81). A new study by Bambauer and colleagues in Boston found that a simple intervention of faxed alerts regarding patient adherence was not successful in improving antidepressant adherence (11).

The Clinician's Responsibility in Promoting Adherence

Of all those who discontinue medication, 60% have not informed their doctor by three months, and a quarter have not done so by six months (41,42). In fact 90%

of decisions to discontinue are made by the patient without discussion with the doctor (17). Rather than being a cause of therapeutic nihilism, this should be a reason to help the patient understand both the benefits and hazards of antidepressants. More than half of patients who start an antidepressant prescription are hoping for a different treatment or are ambivalent about their treatment preferences (17).

All clinicians must maintain a high index of suspicion for possible treatment-emergent problems (adverse events and missed medication), but this should be communicated in a supportive rather than doubting manner. Simply discussing the *possibility* of an adverse event with the patient reduces the rate of unanticipated discontinuation by half. Similarly the chance of discontinuation is about 60% lower in patients who are simply told to take medication for at least six months compared with those who did not recall being given this information (82). Most patients with depression want to be involved in decision making (83,84). Indeed there is some evidence that adherence improves if more relevant information is given (85) or if patients are involving in treatment decisions (86). Quality of care for depression is improved not only when patients participate more actively but also when physicians explore and validate patient concerns (87). Yet analysis of doctor-patient discourses illustrates that clinicians ask approximately one of five patients how well his/her antidepressants are working, and only 1 of 10 patients if he/she is experiencing any side effects (88). After analyzing audio recordings of interactions between 152 clinicians (internists and primary care) and patients, Young and coworkers (2006) discovered a mixed picture of communication (89). Whereas drug purpose and side effects were usually mentioned, barriers to use and "what to do if you missed a dose" were mentioned less than 2% of the time. Further, advice to continue to take the medicine even if feeling better and advice to continue to take the medication until further review were discussed on only 5.4% and 3.9% of the visits, respectively. Clinicians provided information about antidepressant treatment duration in 35% of interactions, which is interesting because Bull's group (44) previously found that although 71% of clinicians claimed to specify treatment duration, 64% of patients recalled no such instructions. This has led some to suggest that it is the practitioner's behavior that is the major remediable barrier to poor concordance (90).

Brown and colleagues (2007) used the Patient Education Questionnaire (91) to measure clinician advice (92). When measured by the percentage of prescribed doses taken, adherence was 82% at one month and 69% at three months. When measured by the percentage of days with correct intake and timing, adherence was only 55% at one month and 43% at three months. Several key messages about antidepressant medication differentiated adherent from nonadherent patients including "told what to do if there were questions," "keep taking the medication even if feeling better," and "told how long to expect to take medicine," advised of how long side effects will last, and "given advice on managing minor side effects" (Fig. 2). The odds of being adherent (measured by doses) more than tripled among those who said they were told "how long to expect to take the medicine" and "told what to do if there were questions" and the odds of being adherent (measured by days) doubled among patients who reported that they were "told how long to expect to take the medicine" compared with those who said they had not been.

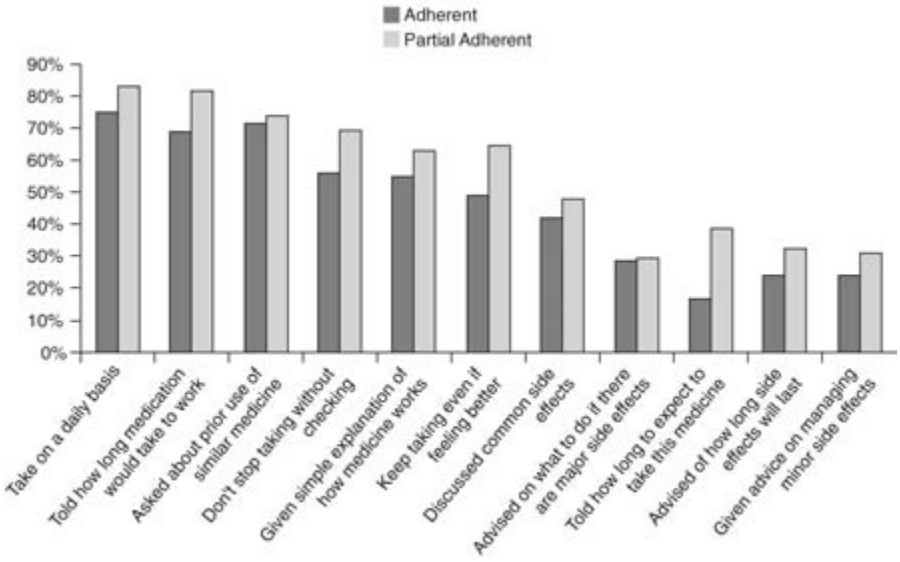

FIGURE 2 Frequency of clinician advice about starting antidepressants. *Source*: Adapted from Ref. 92.

DISCUSSION

Most, perhaps all, patients have difficulty taking medication for a long period of time. Depression management often necessitates taking antidepressants for 6 or 12 months and occasionally when the risks of relapse are very high, indefinitely. In clinical practice about half of antidepressant users have been taking their medication for a prolonged period and can be considered long-term users (93). Difficulties with antidepressants include not only problems with efficacy and tolerability, but poor understanding of the necessity of treatment fueled by often inadequate explanations from clinicians and inadequate follow-up thereafter. Recent evidence suggests that the majority of patients prescribed an antidepressant will experience some kind of problem that will lead to thoughts of discontinuation. Further, many miss doses because of simple lapses or inconvenience, and many will stop taking their medicine once they feel well. Although this may be associated with adverse outcomes in terms of relapse or readmission, missing doses and even stopping completely may be the most rational approach to health, given patients understanding of their illness and the information available to them (94–96). Most of the antidepressants are not prescribed by psychiatrists, and adherence issues may be more problematic in this group for a variety of reasons (97). About a quarter of those taking antidepressants appear to have no identifiable psychiatric disorder. Adherence habits in this group remain unclear.

Clinicians who are alert to these types of difficulties or who receive specific feedback may prevent unmonitored discontinuation (98). Clinicians who are able to discuss the strengths and weaknesses of medicines and who appear to be open to feedback will foster greater trust and therapeutic alliance. At the

same time patients who have difficulty remembering to take their medication might be helped by simple reminder systems. Both partial nonadherence and discontinuation can be helped by enhanced collaborative care for depression.

Finally, it takes time to develop rapport with patients, trust, and antistigma toward antidepressant use. It also takes time to cover in a full supportive, psychoeducational model what a patient's diagnosis is, which of several treatment options is available, what the adverse effects of each is, how long to adhere to treatment, etc. There is a growing trend in psychopharmacology to see patients more quickly in the "medical model." It is not uncommon for a psychiatrist to see a patient every 10 to 15 minutes in some practices. This is akin to a primary care physician spending 30 minutes with a patient discussing several medical problems, including depression. The net effect is that there are too few minutes available for specialist or generalist alike to modify and enhance clinician variables likely to enhance compliance and ultimately treatment outcome. This data about nonadherence is sobering, and it is the editor's hope that clinicians are encouraged to spend more time with patients, that is, quality instead of quantity to promote better outcomes. Readers will notice in further chapters that use of guidelines, algorithms, and rating scales may also allow better outcomes in depressed patients and these take more visit time as well. If we are to seriously look at how antidepressants underperform, that is, remission in only one-third of patients who are noncomorbid in clinical trials, then improving outcomes with compliance-enhancing techniques, algorithms, and rating scales should be embraced at the expense of seeing too many patients too quickly for secondary reasons.

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5 Algorithms: STAR*D, Positives, Negatives, and Implications for Clinical Practice

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INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent mental illness that poses a hazard for the affected individuals, their respective family, and society at large. Results from multiple cross-national epidemiological studies indicate that the lifetime prevalence of MDD in Western societies is approximately 10% to 20% (1). MDD often pursues an episodic course without inter-episodic recovery; a bimodal age of onset is observed with peaks in early and mid-late adulthood. Individuals with MDD are differentially affected by both psychiatric (e.g., anxiety and substance use disorders) as well as disparate general medical conditions (e.g., cardiovascular disease, type II diabetes mellitus) (2).

According to the World Health Organization (WHO), MDD is the fourth leading cause of disability-adjusted life-years (DALYs), and is projected to be second only to ischemic heart disease by the year 2020 (3). Unipolar depression accounts for 11% of the global years lived with disability (YLDs). Moreover, the rate of suicidality (i.e., attempts, completions) is increased 10- to 20-fold in MDD populations when compared with the general population (4,5). A concatenation of results from cost of illness studies indicates that mood disorders are the most costly behavioral health conditions in the United States.

During the past decade, the deleterious effect of MDD on work productivity and health service utilization has become increasingly apparent as the economy shifts toward a greater emphasis on "human capital." For example, a primary care survey orchestrated by the WHO reported that individuals with MDD are likely to report significant rates of workforce disability due to the effects of absenteeism and presenteeism (6). Similar conclusions have been documented elsewhere (7). Several studies evaluating the effect of MDD on general and specialty medical service utilization have buttressed the notion that affective disorders presage service utilization directly as well as increase utilization for other medical conditions when MDD is comorbid (8,9). The overarching therapeutic objective in the management of MDD is to reduce the overall burden of illness to the affected individuals, their family/dependents, as well as society at large. Toward this aim, timely detection and implementation of chronic disease management principles (e.g., decisions support, patient self-management) is warranted. Results from both efficacy and effectiveness trials indicate that rates of treatment nonresponse and nonrecovery are significant in MDD. Taken together, individuals with treatment-resistant depression (TRD)

account for a disproportionate percentage of the overall burden of illness attributable to MDD. Improving strategies to more reliably abrogate depressive symptoms and restore psychosocial function in TRD populations holds promise to substantially reduce overall burden of illness in MDD.

TREATMENT-RESISTANT DEPRESSION

TRD is an appellation that has been often employed interchangeably with chronic depression and severe depression despite the fact that these are overlapping yet distinctly different phenotypes. Chronic depression refers to a major depressive episode of duration $\geq$2 years. Severe depression has been variably defined; often cited definitions are a HAMD-17 score $\geq$ 28 or a MADRS score $\geq$ 30 (10). In many cases, individuals with chronic and/or severe depression appear as "pseudoresistant" largely on the basis of insufficient treatment duration and/or intensity. TRD, however, has often been defined as persistence of impairing depressive symptoms despite a minimum of two adequate antidepressant trials. Before the appellation TRD is assigned, practitioners must ensure appropriate diagnosis, patient adherence to treatment, and optimization of the index trial (Fig. 1). An adequate duration of antidepressant therapy is generally considered to be four to six weeks, although results from effectiveness studies indicate that longer trial durations may be accompanied by a higher percentage of symptom

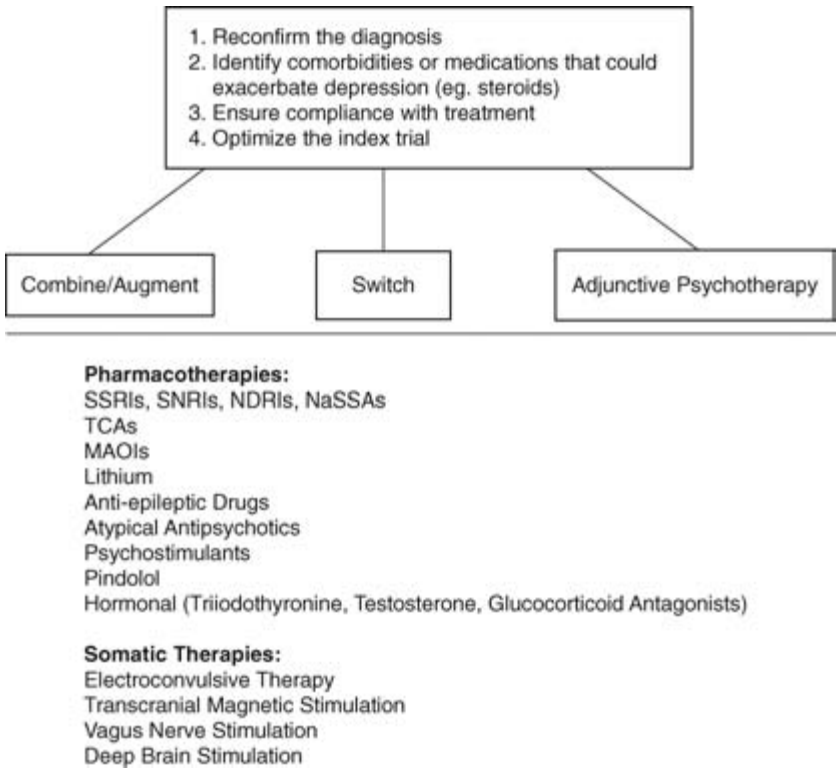

FIGURE 1 Steps to take when apparent treatment failure occurs.

remitters (11–15). If symptomatic objectives are not achieved with an index antidepressant therapy, the probability of achieving remission may be increased with subsequent strategies that include combination/augmentation, switching, or the adjunctive/alternative use of cognitive behavioral therapy (CBT) (16).

TREATMENT ALGORITHMS: THE STAR*D TRIAL

Background

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial is the largest study ever conducted that compared algorithmic treatment effectiveness in "real-world" patients experiencing a major depressive episode in MDD (17–23). It is a five-year study, supported by the National Institute of Mental Health that included over 4000 subjects. Several unique methodological features reify the ecological validity of this study including, but not limited to, the enrollment of both public and privately insured patients, the recruitment of subjects in primary and specialty care settings, the broad inclusion criteria, the use of pharmacological and psychosocial (i.e., CBT) treatment options, and the so-called clinical equipoise randomized design.

The overarching question that the STAR*D trial aimed to address was "What is the treatment of next choice in individuals failing to achieve remission with index antidepressant therapy?" Toward that aim, the STAR*D trial evaluated multiple pharmacological treatment options as well as CBT administered as augmentation/combination or switch strategies (Fig. 2). The treatment options chosen for evaluation in the STAR*D trial were selected on the basis of extant literature and clinical experience with patients who have presented with TRD.

The primary outcome measure in the STAR*D trial was remission, operationalized as a HAMD-17 score of ≤ 7. At each step in the algorithm, a 12- to

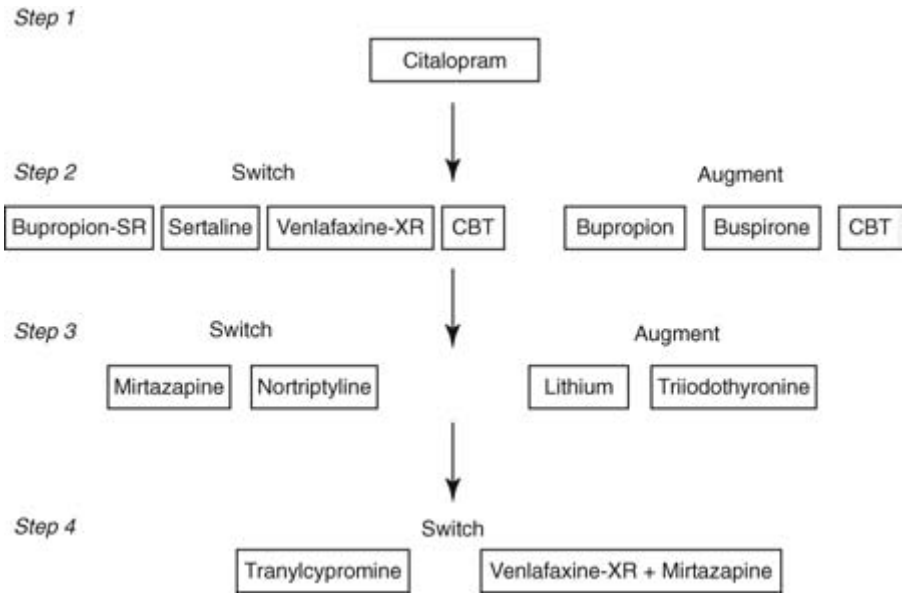

FIGURE 2 Treatment algorithm in the STAR*D trial.

14-week treatment trial was provided. If symptomatic remission was not attained after this treatment duration, individuals were allowed to proceed to the next step of therapy. Those who achieved remission were enrolled into a 12-month follow-up observation period for relapse surveillance (corresponding to HAMD-17 $\geq$14) (Fig. 2).

As decision support and the use of clinimetrics in the management of chronic diseases improve treatment outcomes, all participating centers employed "measurement-based care." This refers to the routine use of rating scales, systematic monitoring for adverse events, and guideline-informed antidepressant dosing.

A novel aspect of the STAR*D trial was the use of a clinical equipoise randomized design. The idea was to simulate the clinical setting by including the element of patient preference. In this type of study design, participants were allowed to eliminate the possibility of being randomized to treatments, which they deemed to be unacceptable. For example, individuals may elect to be randomly assigned to switch or augmentation therapies only. Moreover, subjects who preferred CBT versus a pharmacological treatment strategy were offered only the psychosocial treatment. The shared decision making regarding treatment assignment resembles real-world clinical practice.

Results

Step 1

Citalopram monotherapy (mean exit dose 41.8 $\pm$ 16.9 mg/day) resulted in a remission rate of 28% (17). For those who achieved remission, the mean time to this endpoint was 6.7 weeks. Although a large proportion of this group achieved remission within the four- to six-week period, which is the recommended trial duration according to clinical practice guidelines, a substantial remainder did not achieve remission until much later (24–27).

Factors associated with a higher probability of remission were being Caucasian, female, employed, and better educated, as well as earning higher levels of income. In contrast, a lengthy index episode of depression and having multiple comorbidities were associated with a lower likelihood of remission.

Step 2

Switch randomization strategies for those who failed to achieve remission in step 1 included sustained-release bupropion, sertraline, and extended-release venlafaxine. The remission rates for these medications were 21% (mean exit dose 282.7 $\pm$ 104.4 mg/day), 18% (135.5 $\pm$ 57.4 mg/day), and 25% (193.6 $\pm$ 106.2 mg/day), respectively, which were not significantly different (18). Moreover, there was no significant difference in the overall tolerability profile between agents, although the type of adverse events recorded was not identical for each agent. Taken together, the observation of similar symptomatic outcome with a "classmate" antidepressant when compared with a between-class switch provides empirical evidence against a popularly held notion that switching class antidepressants would improve the probability of remission in an individual who is an SSRI non-remitter.

The augmentation strategies that were compared were sustained-release bupropion and buspirone. Remission rates were 29.7% (mean exit dose 267.5 $\pm$ 99.8 mg/day) and 30.1% (40.9 $\pm$ 16.7 mg/day), respectively (19). Although there

were no significant differences between groups on the primary outcome measures, sustained-release bupropion was associated with a greater reduction in secondary depression measures (quick inventory of depressive symptomatology self-rated; QIDS-SR) and a lower dropout rate due to intolerability when compared with adjuvant buspirone.

Taken together, remission rates with "next-step" treatment (level 2) were approximately 25%, resulting in an aggregate remission rate of approximately 50% to 55% after two sequential treatment interventions. These results underscore the importance of initiating treatment strategies with the greatest therapeutic potential early in the treatment course when the velocity of symptomatic change is likely to be the greatest.

Individuals who received CBT either as a switch or augmentation strategy had similar remission rates to those who received pharmacotherapy (20). However, augmentation with pharmacotherapy resulted in a faster onset of remission when compared with adjuvant cognitive therapy. As one might have suspected, a switch to an alternative antidepressant resulted in a higher occurrence of adverse events when compared with those receiving CBT alone.

Step 3

The switch strategies at this level compared mirtazapine and nortriptyline. Remission rates were reported as 12% (mean exit dose 42.1 ± 15.7 mg/day) and 20% (96.8 ± 41.1 mg/day), respectively. Again, there were no statistically significant differences in treatment outcomes and/or overall tolerability on between-group comparisons (21).

The augmentation strategies compared at step 3 were lithium and triiodothyronine (T_3). Remission rates were 16% (mean exit dose 859.8 ± 373.1 μg/day) and 25% (45.2 ± 11.4 μg/day), respectively, a nonsignificant difference (22). Lithium treatment, however, was associated with a higher frequency of overall adverse events compared with T_3, suggesting a relative advantage for T_3 in its relative therapeutic index.

Step 4

At this level, tranylcypromine monotherapy was compared with venlafaxine/mirtazapine combination. The remission rates were 7% (mean exit dose 36.9 ± 18.5 mg/day) and 14% (210.3 ± 95.2 mg/day or 35.7 ± 17.6 mg/day), respectively (23). Tranylcypromine was associated with a higher rate of discontinuation due to intolerability. In the context of similar efficacy between groups, a therapeutic advantage may be afforded by employing venlafaxine/mirtazapine combination. Moreover, the use of venlafaxine/mirtazapine combination does not warrant dietary restrictions.

Discussion

The STAR*D trial provides empirical evidence for rational decision making in the management of MDD in the primary care setting. The therapeutic principles for managing a major depressive episode that fails to remit with an initial antidepressant agent include clarifying the principal diagnosis, identifying and treating comorbidities, eliminating medications and other substances that may exacerbate depressive symptoms, ensuring adherence to treatment, and optimizing the index trial. If these strategies fail, then combining/augmenting and/or adjunctive/alternative CBT may be considered (16).

The optimal trial duration for antidepressant therapy is generally considered to be approximately four to six weeks according to most evidence/consensus-based guidelines for the treatment of a major depressive episode (24–27). Results from the STAR*D trial indicate that a longer trial duration may be required to achieve full therapeutic effect (15). Of all participants who achieved remission after the first step of treatment, up to 50% reached this primary endpoint after week 6 (17). Hence, discontinuing therapy prior to six weeks may be premature. The suggestion for a longer index trial needs to be considered in the context of patient acceptance of ongoing treatment despite the lack of meaningful therapeutic benefit (15). For example, most individuals not remitting after four to six weeks of therapy are unlikely to be willing to pursue an additional six to eight weeks in the absence of any symptomatic benefit and possible presence of antidepressant-associated adverse events.

In the STAR*D trial, the probability of achieving remission decreased as a function of the number of treatment interventions attempted (28). The remission rates at steps 1, 2, 3, and 4 in the treatment algorithm were 28%, 25%, 18%, and 10%, respectively. Thus, 53% of patients can be expected to achieve remission after two sequential therapeutic trials, and 81% can be expected to achieve remission after four sequential therapeutic trials if these algorithmic steps are followed.

The STAR*D trial found that multiple patient characteristics were associated with the likelihood of remission. These include being Caucasian, female, and married; attaining higher education and higher economic status; and having private insurance, fewer concurrent general medical and psychiatric conditions, better overall physical and mental function, greater life satisfaction, and a shorter index episode (17). In contrast, being unmarried or living alone and having longer index episodes, more general medical and concurrent psychiatric disorders, lower baseline function, and lower quality of life were associated with lower remission rates.

Interestingly, participants who required multiple therapeutic steps before achieving remission also showed a greater tendency for relapse (28). Physicians working with these treatment-resistant individuals need to be aware of the increased risk of relapse and the need for careful surveillance for signs and symptoms that may indicate relapse of depression.

The follow-up results revealed that participants who achieved remission were less likely to relapse than participants who simply improved symptomatically. When participants who achieved remission status at entry into the follow-up phase were compared with participants who elected to enter the follow-up period after simple symptomatic improvement, the relapse rates at step 1, 2, 3, and 4 were 34%, 47%, 43%, and 50%, respectively, versus 59%, 68%, 76%, and 83%, respectively (28). Thus, residual depressive symptoms seem to predispose and portend subsequent relapse in depression (26,29–31). These observations support the expert consensus that remission should be the goal of acute treatment.

Several lines of evidence indicate that achieving symptomatic remission is associated with a more favorable symptom, functional, humanistic, and economic outcome in MDD. For example, individuals who achieved remission in the STAR*D trial experienced a longer symptom-free interval to relapse when compared with individuals who did not achieve acute remission. The time to relapse at steps 1, 2, 3, and 4 were 4.4 months, 4.5 months, 3.9 months, and

2.5 months, respectively, for the former (remitters) versus 3.6 months, 3.2 months, 3.0 months, and 3.5 months, respectively, for the latter (non-remitters) (28). These observations provide additional support for the consensus statement that remission should be the goal of acute treatment even if multiple treatment attempts are required. With regard to whether switching or augmentation/combination would be the more appropriate step after failure of one antidepressant, the STAR*D trial did not address this question because of the limitations of the clinical equipoise randomization design.

It is worth noting that treatment outcomes in the STAR*D trial may exceed outcomes typically encountered in routine clinical care. The use of measurement-based care approach may account for this. The utilization of depression-rating scales, guidelines for dose adjustments, and training of clinicians allows for better precision in the assessment of illness severity, treatment response, and timing of interventions, which likely accounts for the improved treatment outcomes (28). Several brief rating scales for depression have been published. These include but are not limited to the QIDS, the Patient Health Questionnaire (PHQ-9), and the seven-item HAMD (32–34).

To summarize, the STAR*D trial provides real-world generalizable results regarding the treatment of depressed individuals in primary care. Results from this trial support remission as the goal for treatment of acute depression. The STAR*D trial also identifies individuals at risk for TRD, and compares the effectiveness of multiple therapeutic interventions in stepwise fashion. Unanswered questions from the STAR*D trial and directions for future research include whether combination treatment should be initiated as first-line therapy for depression, what the role is for atypical antipsychotics in the symptomatic treatment of depression, and what constitutes the optimal duration of maintenance treatment for individuals achieving remission. Moreover, individuals in the STAR*D trial began treatment with antidepressant pharmacotherapy; outcomes in individuals who begin with a psychosocial intervention (e.g., CBT) may exhibit different response patterns with subsequent treatment interventions.

ALTERNATE THERAPIES FOR TREATMENT-RESISTANT DEPRESSION

Although the STAR*D trial is the largest study to compare competing treatment options in the stepwise management of major depressive episodes, several treatment alternatives utilized in clinical practice were not included in the STAR*D trial.

Electroconvulsive therapy (ECT) has consistently demonstrated significant response rates after acute treatment. For example, clinical studies have documented response rates ranging from 60% to 80% with ECT (25). A major limitation of ECT is the enduring cognitive deficits reported by a substantial percentage of treated individuals as well as high rates of relapse/recurrence.

Transcranial magnetic stimulation (TMS) is an alternative neuromodulatory intervention that demonstrates significant response rates in disparate populations. Advantages of TMS relate largely to its relative ease of administration, the avoidance of anesthesia, and sparing of cognitive impairment. However, the overall effect size of TMS may be inferior to ECT in highly resistant MDD populations. Nevertheless, optimal parameters and application of TMS need to be refined until definitive statements regarding its absolute or relative efficacy can be strongly pronounced (35).

Experimental approaches to TRD include magnetic seizure therapy, vagus nerve stimulation, and deep brain stimulation. Several reports have appeared regarding the efficacy of DBS in patients with highly recalcitrant MDD (36,37). This technique is commonly used in the treatment of end-stage Parkinson's disease. Preliminary results indicate promising outcomes in both symptomatic and functional domains. Larger randomized multisite, blinded clinical trials will provide further evidence confirming or refuting DBS efficacy.

Alternative pharmacological strategies include psychostimulants, pindolol, anticonvulsants, hormonal-based therapies (e.g., glucocorticoid antagonists), and atypical antipsychotics (38–41). During the past decade, the evidence supporting the use of atypical antipsychotics in the treatment of nonpsychotic unipolar depression and TRD as both monotherapy and adjuvant treatment approaches has become better established (42,43). For example, aripiprazole has received an indication by the U.S. Food and Drug Administration as an augmentation strategy to antidepressant therapy in individuals insufficiently responsive to index treatment. Moreover, olanzapine in combination with fluoxetine offers an improved therapeutic outcome in individuals failing multiple antidepressant therapies. Quetiapine is the most extensively studied atypical antipsychotic in MDD. Compelling evidence indicates that quetiapine monotherapy is superior to placebo and comparable to conventional unimodal antidepressants in the short- and long-term treatment of nonresistant MDD. On several secondary outcomes (e.g., onset of efficacy), quetiapine may have an advantage over conventional agents. Moreover, adjunctive quetiapine therapy has been demonstrated to improve outcomes in antidepressant nonresponders (44). A limitation of quetiapine, olanzapine, and several other atypical antipsychotics is their propensity for metabolic-associated adverse events.

Taken together, TRD is not synonymous with severe depression and/or chronic depression. Nevertheless, there is substantial phenotypic overlap between these disparate entities. Individuals with TRD are disproportionately affected by morbidity associated with MDD. Results from the STAR*D trial provide the largest empirical basis to inform treatment decisions. A "window of therapeutic opportunity" is suggested by results of the STAR*D trial inviting the need for early detection, diagnosis, and deft use of proven agents with the greatest therapeutic potential. The employment of chronic disease management with measurement-based care as an active component may reduce the overall rate of treatment resistance. Several novel psychopharmacological approaches are becoming available for TRD. The largest quantity of data supports the use of atypical antipsychotics. A variety of neuromodulatory approaches (e.g., ECT, TMS) represent treatment alternatives, while results from DBS look promising for individuals with highly malignant TRD.

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6 Measurement-Based Care and Outcome Measures: Implications for Practice

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LACK OF MEASUREMENT WHEN TREATING DEPRESSION IN CLINICAL PRACTICE—AN INADEQUATE STANDARD OF CARE

Imagine going to your primary care doctor with fever and symptoms of an upper respiratory tract infection. Your primary care provider puts his or her palm to your forehead and agrees that you feel warm. A course of treatment is recommended, you return in a couple of days, and he or she again feels your forehead and notes that you are cooler. Would you be happy with this approach toward care? Would you continue to see a doctor who evaluated your body temperature in this way? We would not accept this level of care from an internist, family practitioner, or pediatrician, and yet this is the community standard of care provided by most behavioral health clinicians when treating depression.

To determine the impact of treatment it is necessary to evaluate outcome. In mental health clinical settings this typically is based on unstructured interactions that yield unquantified judgments of progress. This is at variance with other areas of medical care in which outcome is determined, in part, on the change of a numerical value. Body temperature, blood pressure, cholesterol values, blood sugar levels, cardiac ejection fraction, and white blood cell counts are examples of quantifiable variables that are used to evaluate treatment progress. In the mental health field, standardized, quantifiable outcome measures exist for most major psychiatric disorders, yet they are rarely used in routine clinical practice. Thus, to determine the impact of treatment is not simply a matter of *evaluating* outcome, but rather a matter of *measuring* outcome.

During the past three decades more research has been conducted on depression than any other psychiatric disorder. The clinical and public health significance of depression was heightened by the results of the Medical Outcomes Study, which found that depression was more impairing than other chronic medical disorders such as arthritis, diabetes, and hypertension, and as impairing as cardiovascular disease (1). The importance of depression as a public health problem was reinforced by the Global Burden of Disease study, which predicted that by the year 2020 depression will be the second leading cause of death and disability worldwide (2). Depression is the most frequently treated specific psychiatric disorder (3), and antidepressants are among the most frequently prescribed medications in all of medicine. The direct and indirect costs of depression have by now likely exceeded $100 billion (4). And yet, despite its high prevalence, high morbidity, and high consumption of health care resources, the standard of care for evaluating the efficacy of treatment for depression in clinical practice is based on unquantified, nonstandardized clinical impressions.

During follow-up care, judgments of outcome in treating depression are often founded on broad-based, global questions such as "How are you feeling?" or "How are you doing?," inquiries that are similar to every day discourse when greeting a friend or acquaintance. Correspondingly, patients often reply with global, oftentimes misleading, responses such as "Okay" or "Fine." We have seen patients in our offices who, at the beginning of the visit, indicate that they are "fine," and by the end of the visit we agree that hospitalization is warranted. Although hospitalization of depressed outpatients is not common, more common are the patients who indicate that they are "fine," when in fact they continue to experience several symptoms of depression. Thus, the lack of systematic assessment, or measurement, can impede treatment outcome because clinicians, unaware of an inadequate or incomplete treatment response, will incorrectly conclude that no changes in treatment are needed. If clinicians are not making appropriate treatment recommendations, then outcome is likely to be poorer. Routine measurement of outcome with reliable and valid instruments may improve outcome by providing clinicians with information that will enable them to modify their treatment approach with the individual patient. The results of two surveys done by Gilbody et al. and Zimmerman and McGlinchey, however, suggest that standardized scales are not being used to evaluate outcome in clinical practice.

Gilbody et al. (5) surveyed 340 psychiatrists in the United Kingdom regarding their use of outcome measures. Only 11.2% of the psychiatrists routinely used standardized measures to assess outcome when treating depression and anxiety disorders. More than half of the clinicians indicated that they never used standardized measures to evaluate outcome. The authors did not ask the respondents why they were disinclined to use scales to measure outcome; however, they noted that several respondents included comments on the questionnaires, indicating that they thought such scales were simplistic, not useful in clinical practice, of questionable reliability and validity, or overly burdensome and costly to implement routinely.

Zimmerman and McGlinchey (6) conducted a similar survey of 314 psychiatrists in the United States. They too found that the vast majority of psychiatrists did not routinely use scales to monitor outcome of treating depression (Table 1). More than half of the psychiatrists indicated that they never or rarely used scales to monitor outcome, and less than 10% almost always used scales to monitor outcome of depression treatment. They compared the characteristics of psychiatrists who reported using scales frequently or almost always to the rest

TABLE 1 Reported Frequency of Use of Standardized Scales to Measure Outcome in the Treatment of Depression by 314 Psychiatrists Attending a CME Conference

Frequency	Percentage	*N*
Never	28.8	88
Rarely	32.0	98
Sometimes	21.2	65
Frequently	11.4	35
Almost all the time	6.5	20

Data were excluded for 8 subjects because either the data were missing ($n = 7$) or more than one response was checked ($N = 1$).

TABLE 2 Reasons Given by Psychiatrists for Not Using Standardized Scales to Measure Outcome in the Treatment of Depression ($n = 248$)

Reasons	Percentage	*N*
Do not believe it would be clinically helpful	27.8	69
Do not know what measure to use	20.6	51
Take too much time	33.9	84
Too disruptive of clinical practice	19.0	47
Were not trained to use them	34.3	85
Other	28.6	71

Three subjects who indicated that they never, rarely, or sometimes used scales did not respond to this question.

of the group and found no difference between the two groups in gender, age, years of practice, or practice setting.

Subjects who reported never, rarely, or only sometimes using scales to monitor outcome were asked the reasons for not routinely using scales in their clinical practice. More than one-quarter of the subjects indicated that they did not believe using scales would be clinically helpful, that they take too much time to use, and that they were not trained in their use (Table 2).

The results of these two surveys showed that psychiatrists typically do not use standardized scales of established reliability and validity when treating patients with depression. One issue identified as an obstacle in their use is the perceived burden of scale completion. If the payers of the delivery of mental health treatment increasingly encourage, or require, the measurement of outcome, then the user-friendliness of measurement tools, as well as their reliability and the validity, will be critical to their widespread adoption. Clinicians are already overburdened with paperwork, and adding to this load by requiring repeated detailed evaluations with such instruments as the Hamilton Rating Scale for Depression (HRSD) (7) is unlikely to meet with success. Self-report questionnaires are a cost-effective option because they are inexpensive in terms of professional time needed for administration, and they correlate highly with clinician ratings. To be sure, there are also limitations with self-report questionnaires such as response set biases, and their use may be limited by the readability of the scale and literacy of the respondent. However, self-report scales are free of clinician bias and are therefore free from clinician overestimation of patient improvement (which might occur when there are incentives to document treatment success).

Suggestions of the beneficial impact of measuring outcome come from the STAR*D trial, the largest study of the treatment of depression ever conducted. In the acute phase component of STAR*D, during which patients were treated with citalopram for up to 12 weeks, the rates of response and remission were similar to rates typically reported in controlled efficacy studies. Trivedi and colleagues (8) suggested that an adequate treatment response might have been more difficult to achieve in STAR*D than typical industry-funded efficacy studies because patients with comorbid disorders, who are less responsive to treatment, were not excluded. They attributed the better-than-expected (albeit modest) response and remission rates to the adoption of a system of measurement-based care. That is, they indicated that the use of frequent, standardized, quantitative assessments to guide treatment decision making contributed to an increased

likelihood of a positive outcome, and they recommended that a measurement-based care approach toward clinical management be adopted in routine clinical practice.

Some schools for psychotherapy for depression advocate routine use of measurement to evaluate outcome. For example, the use of self-report scales such as the Beck Depression Inventory to evaluate treatment progress is an integral component of cognitive therapy for depression (9).

The call for measurement-based care is consistent with the recent Center for Medicare and Medicaid Services Physician Quality Reporting Initiative, which is intended to increase clinicians' motivation to systematically evaluate outcome by providing financial incentives to monitor outcome. At present, the level of financial incentive is modest (1.5% of fees).

One Reason Why Measurement May Be Important in Treating Depression—Improved Detection of Residual Symptoms

Would a physician treat diabetes without measuring glucose levels? Or treat hypertension without measuring blood pressure? Or treat a febrile illness without measuring body temperature? Of course not. Measurement provides the clinician with information regarding the degree and completeness of treatment success, and suboptimal outcome in the treatment of diabetes, hypertension, hypercholesterolemia, or an infection would prompt intervention. The same should be true in the treatment of depression.

Research has consistently demonstrated that residual symptoms of depression in patients who have been identified as treatment responders are at increased risk for relapse. For example, Paykel and colleagues (10) followed up 64 treatment responders for 15 months. Treatment response was defined as failure to meet full major depression criteria for two months. Patients who scored above 8 on the HRSD were three times more likely to relapse during the follow-up interval than patients scoring 8 or below (76% vs. 25%). Thase et al. (11) followed 48 depressed patients who responded to 16 weeks of cognitive-behavior therapy for one year after the completion of treatment. Responders scored 10 or less on the HRSD, and their scores improved at least 50% from baseline. The responders were subdivided into those who did and did not score 6 or less on the HRSD for the last two months of treatment. Patients who scored 6 or less were significantly less likely to relapse than patients who scored 7 through 10. Several other follow-up studies have similarly found that the presence of residual symptoms in patients who responded to treatment predicted poorer outcome (12–14).

The data are clear—the presence of residual symptoms in depressed patients who have improved with treatment predicts poorer long-term outcome. How well do clinicians detect such residual symptoms? We are not aware of studies that have addressed this question. However, as demonstrated in the STAR*D study, residual symptoms are common. Trivedi et al. (8) found that two-thirds of the patients experienced mild-moderate levels of symptoms at the end of the acute phase of treatment with citalopram. To be sure, the remission rate during the acute phase in the STAR*D trial was modest despite the use of measurement to guide treatment decision making. However, cumulative remission rates after multiple levels of treatment are greater than 60% (15,16), and we agree with the STAR*D researchers' speculation that quantified

measurement enhanced outcome because incomplete response could not be ignored. In other words, if a clinician detects an abnormal laboratory value (or rating scale value), then he or she is more likely to investigate further and be more aggressive in treatment. This assumes that more aggressive or complete treatment will render better outcomes.

Changing the standard of care in the treatment of depression to incorporate a validated assessment tool would raise the standard to the level accepted in the treatment of other chronic medical disorders such as diabetes and hypertension. The use of a measurement tool should reduce the likelihood of underrecognition of the residual symptoms, which leave patients at greater risk for relapse, as well as reduce the likelihood of incorrectly concluding that symptomatic patients have positively responded to treatment based on global attestations that they are doing fine or okay.

Other Reasons Why Measurement Might Improve Outcome

Routine outcome assessment with self-report scales can enhance therapeutic effectiveness for different reasons, depending on the stage of treatment. The completion of self-administered scales increases patients' active participation in their care, and this might facilitate participation in other therapeutic activities such as exercise or pleasant activities. Patients who are more active in their treatment, and who believe that their clinicians better understand their clinical status, may be more likely to continue with treatment. Valid symptom assessment may help clinicians identify for patients' areas of improvement that had not been recognized. For example, consider a patient who is still depressed, pessimistic, amotivated, and self-deprecatory and who, at the beginning of the follow-up visit, states that he or she is no better, but who in fact is sleeping better, feeling somewhat more energetic, and concentrating better. Identification of some areas of improvement could reduce patients' therapeutic nihilism, thereby increasing treatment retention. Thus, more accurate symptom assessment might not only improve detection of residual symptoms in patients who report that they are feeling better, but it can also improve detection of mild improvement, which might be a harbinger of future improvement (17–19) in patients who are not yet doing well.

Patients followed longitudinally, over the course of years, may uniquely benefit from routine use of scales. For example, it may be easier to detect seasonal patterns of symptom fluctuation when looking at graphs of symptom scores. Patients who relapse, and distort the effectiveness of treatment by minimizing or overlooking periods of sustained remission because of state-dependent cognitive biases, may be more open to more accurate views of their longitudinal course when shown the forms they had completed months earlier that indicated minimal levels of symptoms.

There are thus multiple theoretical reasons as to why measurement-based care might improve treatment outcome.

PRIOR STUDIES OF THE IMPACT OF MEASUREMENT ON OUTCOME

Several authors have suggested that outcome should be routinely measured in clinical practice (20–22), though recent literature reviews and commentaries on the impact of measurement of outcome have concluded that there is little

evidence for its therapeutic benefit (21,23–25). However, these reviews identified few studies of measurement-based care of the type discussed in the current chapter and instead focused on pretreatment evaluation and screening in primary care.

The few controlled studies on standardized outcome assessment have been conducted on either severe and persistently mentally ill patients or mildly ill clients attending a university counseling center. Slade and colleagues (26) randomized 160 patients to complete on a monthly basis self-report scales assessing needs, therapeutic alliance, and quality of life. Also on a monthly basis clinicians completed a seven-item measure of the severity of the patient's mental health problems, a need appraisal scale, and an alliance scale. After three and six months, the clinicians received information regarding change in scores over time and areas of disagreement between patient and clinician ratings. Half of the patients had schizophrenia or other psychotic disorder. It was not clear if the study was of patients who were presenting for treatment or who had already been in treatment for a sustained amount of time. The authors found no impact of the intervention on patient ratings of quality of life and need, but they found that the number of psychiatric inpatient days was significantly reduced in the intervention group.

A significant methodological limitation of the Slade et al. study was the lack of integration of the assessment intervention into clinical practice. Neither patients nor clinicians completed scales immediately before or during the therapeutic encounter; thus measurement was not directly tied to clinical care. Many of the hypothesized reasons discussed earlier as to why measurement would improve clinical care assume that the results of measurement are overtly being acknowledged and addressed during the clinical visit. We believe that measurement will have its greatest clinical effect if it is integrated into the treatment session. The Slade et al. study was of a diagnostically heterogenous sample, and perhaps for this reason disorder-related symptom measures were not included because there were too many types of psychopathology to consider. We would speculate that the type and severity of symptoms is one of the most important factors influencing treatment decision making.

In contrast to this study of severely ill patients, Lambert and colleagues (27,28) have conducted a series of studies on the impact of measurement and feedback on psychotherapy outcome of mildly ill outpatients. Following the work of Howard et al. (29), a patient's progress was compared to the expected course of symptomatic and functional improvement. The expected level of improvement was based on benchmarking studies of thousands of patients who received psychotherapy in diverse settings and who completed the same outcome measure. From these benchmarking studies "recovery curves" were derived, which graphically illustrated the expected rate and level of improvement. Patients completed the outcome scale before each therapy visit, and a research assistant scored the scale and compared the results to the empirically derived recovery curves. On the basis of this comparison, a colored dot was placed on the patient's chart, indicating the adequacy of improvement. Inadequate levels of improvement were accompanied by a message suggesting that treatment should be either intensified or perhaps changed altogether.

In their initial study, Lambert et al. (27) randomly assigned 609 clients treated in a university counseling center to the feedback or treatment as usual groups. All patients completed the outcome measures. The group was relatively

mild in severity with one-third receiving a V code diagnosis or a diagnosis of adjustment disorder. In the group making inadequate levels of improvement (~10% of the entire sample), those randomized to the feedback condition received significantly more therapy visits than the patients randomized to the no feedback condition, scored significantly lower on the outcome questionnaire at the end of treatment, were more likely to improve by the end of treatment (26% vs. 16%), and were less likely to deteriorate by the end of treatment (6% vs. 23%).

Lambert and colleagues (28) conducted a replication study, again in a university counseling center treating mildly ill clients (more than 40% with a V code diagnosis or adjustment disorder). In this larger study of 1020 clients, those in the feedback condition improved significantly more than those in the no feedback condition, though this difference was limited to clients who did not manifest the expected level of improvement. In the group that did not achieve expected levels of improvement during the course of treatment (approximately 24% of the sample), those in the feedback condition were significantly more likely to have improved by treatment termination (32% vs. 18%). The authors also combined these results with those from their first study and reported that the improvement rate across both studies in the patients failing to achieve expected improvement was significantly higher in the feedback group (30.5% vs. 17.5%), and deterioration rates were significantly lower (15% vs. 23%). As in the initial study, clients in the feedback condition received more therapy sessions. Other studies from this group have been consistent with these initial results (30–32).

Lambert's work has demonstrated that measurement and feedback are associated with improved outcome and can influence therapist's behavior insofar as more therapy visits are conducted with clients who are known to be not doing as well as expected. A limitation of these studies is that all except one small study of 200 psychiatric outpatients (31) have been based on mildly ill clients receiving psychotherapy at a university counseling center. Only one-quarter of the patients were diagnosed with some type of mood disorder (the exact nature of the disorder was not indicated). Also, these studies have ostensibly examined the impact of feedback, not measurement per se. Measurement in the absence of feedback is a sterile, clinically meaningless exercise that perhaps is countertherapeutic. The subjects in the studies by Lambert et al. completed the outcome scale on a weekly basis, and one wonders what the clients in the no feedback group thought when their responses were not discussed in the treatment sessions. Perhaps some clients were frustrated, confused, or dissatisfied with the treatment because the information provided on the outcome scale was not raised in it. In fact, the study by Hawkins et al. (31) included a condition in which patients received explicit feedback on the basis of their questionnaire responses, and they noted that patients were interested in this information.

Measurement-based care approaches need to use scales that are readily interpretable to the clinicians who use them. The study by Lambert et al. relied on research assistants to score the measure and alert clinicians to the results. This approach is cost prohibitive for implementation in clinical practice. As Lambert et al. (28) themselves noted in the conclusion of their first replication study "if client-focused outcome research is to have any applicability, it must remain simple and easy to implement in day-to-day clinical practice."

PRACTICAL CONSIDERATIONS IN CHANGING THE STANDARD OF CARE TO INCLUDE THE USE OF SCALES

If the optimal delivery of mental health treatment ultimately depends on examining outcome, then precise, reliable, valid, informative, and user-friendly measurement is critical to evaluating the quality and efficiency of care in clinical practice. Three consumer types should be considered in the selection of a self-administered outcome questionnaire to be used in routine clinical practice: the patient, the clinician, and the administrator. Patients should find the measure user friendly and the directions easy to follow. The questions should be understandable. And the scale should be brief, taking no more than two to three minutes to complete, so that on routine administration at follow-up visits patients are not inconvenienced by the need to come for their appointment 10 minutes early to complete the measure. This would make it feasible to have the scale completed at each follow-up visit in the same way that blood pressure, cholesterol levels, and weight are routinely assessed in primary care settings for patients being treated for hypertension, hypercholesterolemia, and obesity.

The instrument should provide clinicians with clinically useful information and improve the efficiency of conducting their clinical evaluation; thus, the measure should have practical value to the practicing clinician. Of course, clinicians need to be able to trust the information provided by any instrument they use. Consequently, outcome measures of any kind should have a sound basis in psychometrics, demonstrating good reliability, validity, and sensitivity to change. Clinicians should also find the instrument user friendly: It should be easy to administer, score, and interpret with minimal training.

Clinic administrators likewise want measures to be both reliable and valid and to have high patient and clinician acceptance. Administrators are also concerned about the cost of an instrument, from the perspective of both the purchase price and the cost of labor to score the scale. Thus, an outcome measure, or outcome assessment program, should be inexpensive to purchase and implement.

Finally, we believe that any instrument constructed for use in clinical settings should meet scientific standards for publication in peer-reviewed journals. It is important that a new measure stand up to critical scientific review and be published in the scientific arena so that other investigators may further examine its properties.

ARE YOU USING SCALES TO MONITOR OUTCOME WHEN TREATING DEPRESSED PATIENTS?

We hope that the reader will ask himself or herself the question heading this section. If you are not using a scale to monitor outcome, and the chances are very high that you are not, ask yourself why not. Consumer-friendly, reliable, and valid self-administered questionnaire can improve the efficiency of the clinical encounter and allow clinicians to spend more time discussing topics other than symptoms. In this era when many clinical encounters are 15-minute (or briefer) medication visits, increased efficiency can make the visit more meaningful and beneficial to both clinicians and patients.

There are many self-administered depression scales, though some are less appealing as outcome tools for use in routine clinical practice because they are too long (33–35), lack adequate coverage of the DSM-IV diagnostic criteria

(36,37), are expensive to purchase (33), or are somewhat complicated to score (37). Because of ease of use considerations, we would recommend that either the Clinically Useful Depression Outcome Scale (CUDOS) (38) or the 9-item Patient Health Questionnaire (PHQ-9) (39) be used by clinicians at every visit to monitor the course of depression. Both scales take less than two minutes, on average, to complete, and both assess all of the DSM-IV criteria for major depressive disorder. Because it contains fewer items than the 16-item CUDOS, the PHQ-9 probably takes a little less time to complete. However, the advantage offered by being somewhat briefer is offset by some loss of information. The PHQ-9 adheres to the construction of the DSM-IV criteria; thus compound DSM-IV criteria, which refer to more than one symptom (e.g., insomnia or hypersomnia; increased or decreased appetite), are represented by a single item on PHQ-9. Since treatment decision making might be influenced by whether a patient has insomnia or is sleeping too much, or has a reduced appetite or is eating too much, the PHQ-9 does not capture potentially clinically significant information. However, more important than which scale is used to monitor outcome is that some measure is used. Measures such as the CUDOS or PHQ-9 have clearly identified cutoff scores to identify remission, and therefore should not require any special training to be adopted by nonmental health professionals.

CONCLUSIONS

It is time for the clinical management of depression to more closely resemble the management of other chronic medical conditions, and this means that outcome should be measured in a quantifiable manner at each clinical encounter. There is suggestive evidence that measurement-based care improves outcome, though this has not been studied using a method that can be incorporated into routine clinical care. If measurement-based care is to be adopted in clinical practice, it is essential that it not be burdensome to the practicing clinician. Brief, yet valid, scales exist that can be readily incorporated into clinical practice. Routine assessment is well received by patients (40). If the results of well-designed, randomized controlled studies demonstrate that measurement-based care improves outcome and treatment retention and reduces more costly and intensive levels of service, this could potentially have a profound impact on the treatment of depression in clinical practice because of the ease with which clinicians will adopt this therapeutic care management approach. There may be only limited data suggesting that measurement might improve outcome when treating depression, but there is no reason to wait until the studies have been done to prove the benefit of measurement-based care in the treatment of depression. There is little downside to adopting this approach when treating depressed patients.

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7 Genetics and Depression

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INTRODUCTION

The field of genetics represents one of the most promising approaches to understanding the mechanisms underlying disease and behavior. Over the last several decades, we have moved from thinking of genetic disorders as rare conditions that dramatically affect a small fraction of the population to the understanding that genes influence most aspects of a person's life and death. Well-evidenced examples of this influence include genetic associations with personality traits, cognitive style, temperament, intellect, and of course serious mental illnesses. Our knowledge of the genetic basis for major depressive disorder (MDD) and most other mental illnesses has progressed significantly but remains poorly understood because, in part, of a number of complicating factors relevant to the field of psychiatric genetics.

LIMITATIONS IN PSYCHIATRIC GENETICS

Although the adoption of standardized diagnostic schemes such as the diagnostic and statistical manual for mental disorders (DSM) represented a major advance in clinical psychiatry facilitating uniform nomenclature for descriptive syndromes, DSM is, by definition, non-etiology driven. The limited availability of quantifiable biological markers such as those available in other areas of medicine (clinical laboratory parameters, histopathological findings, etc.) further compromises our ability to explore genetic determinants of mental illness.

Major depression is a syndrome defined by the presence of subjective symptoms and consequent suffering or dysfunction. Aside from its intrinsic challenge to diagnostic consistency, depression is a phenotype that does not follow a classic Mendelian pattern of inheritance. A Mendelian disease runs in families in a strict dominant-recessive or X-linked fashion, and although there are one thousand known disease genes, almost no psychiatric diseases are clearly established among them.

A pattern of inheritance that does not follow a traditional Mendelian model is considered "complex." Complex models commonly posses the following features: (*i*) incomplete penetrance (of those carrying the gene, some may never express the disorder, while others may do so very late in life), (*ii*) phenocopies (the same illness may have a nongenetic cause), (*iii*) heterogeneity (different gene mutations can give the same syndrome), (*iv*) pleiogenic risk (the same gene may confer vulnerability for several distinct disorders such as schizophrenia/autism), and (*v*) multiple susceptibility genes (the higher the complexity of the disorder, the higher the number of genes that would account for only a fraction of the observed phenotype).

TRADITIONAL GENETIC APPROACHES

Segregation studies explore patterns of disease expression in pedigrees that may provide information on the mode of inheritance of a given disorder. Earlier studies suggested against "single major locus" inheritance (1–3). Two subsequent reports were able to reject nongenetic models of inheritance but could not discriminate between single major locus and polygenic inheritance (4,5). In a more recent study focusing on subjects with early life–onset (by age of 25 years), recurrent, nonpsychotic, unipolar MDD: when a restrictive definition of affection status for relatives of probands was used (i.e., requiring recurrent MDD), there was evidence for a non-Mendelian recessive major gene effect, while under a more relaxed definition of affection status (any major affective illness), the best-fitting model implied a co-dominant major locus (6). Given the lack of consistent segregation study findings in MDD, it is presumed that fairly complex models involving multiple genes with different modes of transmission may contribute to disease vulnerability. It has also been hypothesized that other genes may exert a protective influence against MDD.

GENETIC EPIDEMIOLOGY

Findings from modern genetic research involving family, twin, and adoption studies consistently support a familial and genetic influence in depression. There is however a fair amount of variability of results between studies, perhaps due, in part, to the range of ascertainment methods utilized (e.g., family history vs. direct-interview assessments), the selection of proband groups (e.g., parents, children), and diagnostic criteria (e.g., DSM or other methods), among others.

Family Studies

In multiple family studies, the risk of depression in relatives of depressed probands has been substantially and significantly higher than the risk in relatives of normal controls, with relative risks ranging from approximately twofold to sixfold (7–10). Family studies have also provided important evidence about clinical features of depression that are associated with greater familiality. Well-replicated reports indicate that the familial risk of depression is inversely related to the age of onset of depression in the proband (11–16). The familial risk of MDD, in particular for early-onset depression, has been replicated in studies of depressed adults, children of depressed parents, and relatives of depressed children (17–22). Similarly, the number of prior depressive episodes in the proband has been associated with a higher familial risk than that for single episodes (23). It may be that individuals with an early age of onset or recurrent unipolar depressive episodes are a more homogeneous group, with potentially greater genetic or other biological factors contributing to their disease status compared with individuals with a single episode. Interestingly as well, rates of MDD are elevated in family members of bipolar-disorder (BD) probands, and rates of BD are elevated in relatives of MDD probands. Although family studies can indicate a familial component for MDD, the underlying genetic contribution cannot be clarified with this method.

Twin Studies

Twin studies represent an important tool to assess the genetic versus the environmental liability for a given disorder. Monozygotic (MZ) twins who posses an

identical genetic load are compared with same sex-dizygotic (DZ) twins who share 50% of their genes. Understanding that most twins share major aspects of their environment, twin studies take advantage of a naturally occurring laboratory to compare concordance rates between MZ and DZ twin pairs for a given diagnosis. Recurrent depression has been associated with a higher ratio of MZ than of DZ concordance (49% vs. 20%) (24). The "heritability estimate" (h^2) is a well-accepted parameter for quantifying the proportional risk of a disorder that is attributable to genetics. Several clinical and population-based twin registries of large size have yielded h^2 ranging from 29% to 75%. The large variability in results is believed to be a consequence of methodological differences like corrections for reliability of diagnosis, assumed population risks, and other variables mentioned above (25–30). Several clinical features have been found to predict co-twin depression, including number of episodes, duration of longest episode, recurrent thoughts of death or suicide, and level of distress or impairment. These clinical features were similarly predictive regardless of sex but had stronger prediction in MZ twins. Some twin studies have also suggested that severity of depressive symptoms and qualitative subtypes, such as "atypicality" of neurovegetative symptoms, and seasonality of mood may be heritable (28,31–33).

Adoption Studies

Adoption studies can also help assess the effect of the environment in the liability to a given disorder by studying affected probands who were adopted at birth and comparing the rates of such disorders in both biological and adopted parents. Despite the limited number of studies reported to have utilized this approach, the findings inconsistently suggest an increase in occurrence of MDD among biological relatives of depressed adoptees (34–37).

MOLECULAR STUDIES

Molecular biology techniques have allowed us to identify the base pair sequences for the entire human genome. Given that the function of a gene is to encode the structure of a specific protein, a mutation by omission, substitution, or insertion of one or more of the bases that form a gene may result in the alteration in function or the absence of a protein. These sequence variations, abundantly observed in the general population, are known as polymorphisms. Polymorphisms can be used as marker loci within a given genetic region. The "linkage" relationship between a disorder and a marker locus suggests genetic influence. Techniques geared to locate disease risk genes in MDD are compromised by the difficulty of assembling the large collections of samples (population based) or families (pedigree based) that would be required to identify susceptibility loci influencing this relatively common, heterogeneous phenotype. Although some large studies of BD have included unipolar MDD in the definition of affective illness, large-scale gene-mapping studies of unipolar MDD itself have not been reported. In an early linkage analysis, sib pairs were used in a linkage analysis of 30 markers in 13 families with MDD without significant results (38). Another linkage analysis of recurrent major depression was conducted in five large Swedish families. They tested linkage to chromosomes 4p, 16, 18, and 21, which have previously been claimed to harbor susceptibility loci for BD, but no evidence of significant linkage was detected either (39). In a study of 34 pedigrees ascertained through probands with early-onset recurrent

unipolar depression, no evidence of linkage or association was found between MDD (or broader affective-disorder phenotypes) and any of 38 polymorphisms in 12 genes related to neuroendocrine or serotonergic systems (40). A more recent study of 656 families with at least one proband with early-onset recurrent unipolar depression revealed an initial linkage peak in the region of human chromosome 15q25.3-26.2 from the genetics of recurrent early-onset major depression (GenRED) research initiative (41). On secondary-analysis after empirical genome-wide correction for multiple testing, results suggestive of linkage were observed on chromosome 17p12 (28.0 cM, excess sharing in male-male and male-female pairs) and on chromosome 8p22-p21.3 (25.1 cM, excess sharing in male-male pairs). The initially identified region on chromosome 15q25-26 was also found as a modest linkage result in a subsequent study (42). This region was fine mapped and reanalyzed, and the finding continued to be supported, suggesting a true linkage of this phenotype to this genetic region (43). The actual genes in this area influencing the phenotype are yet to be determined. The lack of definitive conclusions from classical linkage approaches in MDD in spite of dramatic expansions in size to several hundred nuclear families may be explained by the genetic complexity of the disorder.

Whole-Genome Association Studies

Rather than testing genetic hypothesis, whole-genome association (WGA) studies represent a hypothesis creating method of experimentation, which allows investigation of the entire genome for association between genetic markers and the disease of interest, and do not require prior knowledge about the etiology of the disease. Several WGA studies have already been performed for other psychiatric disorders such as BD (44,45). One interesting study recently assessed genetic association with neuroticism, a common personality trait apparent in depressed individuals (46). Although some statistical significance was found for association to the gene encoding the phosphodiesterase 4A (PDE4A), cyclic adenosine monophosphate (cAMP)-specific protein, it was noted that large samples are needed to detect small effects such as the ones at play in MDD. PDE4A has also been implicated in autism (47), and the larger family of PDE4 genes has associations with schizophrenia (48) and smoking addiction (49). These studies show that novel regions of association, which would not typically by assessed using candidate gene analysis, are contributing to phenotypic variation. Ongoing WGA on MDD and antidepressant response should pave new roads for investigation into the mechanisms of these phenotypes.

Candidate Gene Studies

The Candidate gene approach has become a popular method in the last several years because of its greater likelihood of identifying disease genes in a more feasibly obtainable sample. A candidate gene for MDD is a gene that, on the basis of either its function (protein it encodes for) or its location, might be related to MDD. Although our knowledge of genes important for normal behavior remains limited, there are now substantial data to support the utility of these methods for finding genes that affect illnesses. Thus, candidate gene association approaches are complementary to linkage approaches and may offer advantages like efficiency and sometimes increase knowledge gained about the illness even with negative studies; a positive study may identify a causative gene while

enhancing our understanding of function, rather than just recognizing location. This approach should be utilized with caution given that many well-hypothesized candidate genes have yielded negative results because, in part, of limited sample sizes, phenotypic limitations, and environmental influences (50).

As a result, strategies utilized in other fields of science to deal with complex genetic disorders have also been incorporated to psychiatry. Examples include attempts to reduce genetic heterogeneity by avoiding largely admixed populations, narrow the phenotypic definition by the use of "endophenotypes," modify the phenotypic definition by selecting quantitative traits rather than the traditional categorical diagnosis, and assess the effect of environmental interactions like childhood trauma or recent life stressors. Examples of alternative phenotypes include the use of sensory motor gating, oculomotor function, measures of cognitive processing, and working memory in schizophrenia (51). To narrow the phenotypic scope of "depression," researchers have studied patients with stricter clinical specificity (sub-syndromes), resulting in modest contributions to the genetic understanding of MDD. Newer alternative phenotypes selected on the basis of valid etiological rationale may offer advantages over clinical sub-syndromes. These include neurocognitive findings such as psychomotor dysfunction, impairments in attention, memory, and executive functioning. Biological markers may include electrophysiological abnormalities such as frontal EEG asymmetry; sleep architectural features in polysomnogram like REM latency or ultradian rhythms; structural and functional imaging findings like hippocampal volume, regional cerebral blood flow, and glucose utilization in the amygdala; and response to biological challenges (cognitive or depressive response to neurotransmitter depletions) (52).

The above-mentioned alternative phenotypes may provide better temporal stability supporting the presence of a "trait" quality as opposed to a transitional "state" and may facilitate relevant candidate gene association or linkage findings. Following these principles, several candidate gene association studies in MDD have reported interesting results. To exemplify some of the most commonly cited candidate genes, we will mention some interesting reports involving the 5HT transporter, the tryptophan hydroxylase, and the pro-BDNF gene.

CANDIDATE GENES

On the basis of our current understanding of the mechanisms underlying vulnerability to stress and depression or antidepressant response, many candidate genes have been proposed for their role in the synthesis, transport, recognition, degradation, and regulation of monoamines neurotransmitters [most notably serotonin (5HT)] or a series of intracellular signaling molecules ultimately believed to influence the pathway of neurotrophic signaling [most notably brain-derived neurotrophic factor (BDNF)].

The 5HT serotonin transporter protein (SERT) plays an important role in uptake of 5HT into the presynaptic cell by a sodium-dependent mechanism. The SERT gene solute carrier family 6, member 4 (SLC6A4) is located on chromosome 17. A 44–base pair insertion or deletion polymorphism represents the long (l) and short (s) alleles in the promoter region of the gene (53). In vitro studies suggest that the "l" allele of the polymorphism is associated with higher transcriptional activity, greater levels of SERT m-RNA, and higher uptake of labeled 5HT (53,54). Polymorphic SLC6A4 variation has been extensively studied in a

variety of behavioral phenotypes. Slightly higher scores in neurotic personality traits were initially reported in subjects with the "s" allele. Others failed to replicate these findings. Higher "l" allele frequencies have been reported in depressive-suicide victims and obsessive compulsive disorder (OCD) patients compared with control subjects. Greater depressive response during serotonin depletion has also been associated with the "ll" genotype in remitted depressive subjects (55). Association with "ls" has also been reported in a postmortem sample of MDD (56). Other studies have failed to find any association between alleles of SLC6A4 and mood disorders in European, Japanese, African, and other populations. Highly significant differences in SLC6A4 allele frequency exist between races. Although evidence of an association of SLC6A4 had been inconclusive, a prospective longitudinal study recently found intriguing results. In a sample of 847 Caucasian subjects, Caspi et al. found a significant association of the "s" allele with depression, but this was only in the presence of stressful life events (57). This study is an illustrative example of the challenges observed in psychiatric genetics and the field's increasing methodological sophistication, and improved ability to address relevant variables such as the "nature and nurture" interaction. This finding has been consistently replicated (58–66); however, some studies were unable to replicate these findings (67,68).

Another polymorphism related to SERT is a variable nucleotide tandem repeat polymorphism in intron-2 (Stin-2). Multiple reports of association of this polymorphism and depression-related phenotypes, including evidence for linkage disequilibrium between the intron-2 and the promoter polymorphisms, exist.

The tryptophan hydroxylase gene encodes the rate-limiting enzyme for the synthesis of 5HT, making it an ideal candidate gene to study in depression phenotypes. The allele "A" of the intron 7 (A218C) has been associated with bipolar affective disorder and higher incidence of suicide. The "C" homozygous genotype has lower frequency in unipolar depressives compared with healthy controls. Although transmission disequilibrium test (TDT) studies failed to replicate these findings, a series of reports continue to point attention to this gene and its role in the response to lithium prophylaxis in mood disorders, aggressive disposition, and influence in 5HT turnover rate. Additional polymorphisms have been identified; two in the promoter region of the gene (A6526G and G5806T) are of particular interest. Suicide attempters and completers reportedly have increased frequencies of the haplotype -6526G-5806T-218C. Another marker in intron 3 has also been associated with a phenotype that combines mood, suicidality, and impulsive aggression. An association with a quantitative measure of depression and anxiety, closely related to neuroticism, was found to be associated with a TPH1 genetic polymorphism (69).

An isoform of TPH (TPH2) has recently received considerable attention as it selectively influences the rate of 5HT synthesis in brain (70). Although several variants have been reported for TPH2, the "A" allele of the G1463A polymorphism leads to an amino acid alteration in the TPH2 protein that results in an 80% loss of function (5HT synthesis). The "A" allele was found to be overrepresented in a sample of unipolar depressed subjects (6.9%) compared with bipolar patients and healthy controls (0.9%). The rare allele frequency of "A" in healthy and bipolar subjects suggested a role for this allele in MDD. Most striking was the fact that seven of the nine MDD patients with the "A" allele had treatment-resistant depression and the other two had only responded to high

doses of selective serotonin reuptake inhibitors (SSRIs). Although this report must be replicated, it also speaks of the importance of addressing endophenotypes such as the subpopulation of MDD patients with treatment resistance (71). Unfortunately, these findings did not hold up to replication studies in treatment-resistant MDD (72) or MDD or BD (73). A more detailed investigation of the TPH2 gene structure revealed significant association of a novel polymorphism in the sixth exon of a short isoform of the gene with MDD (74). This finding has clinical implication for all disorders associated with TPH2, as the short isoform has decreased enzymatic activity.

BDNF has been consistently implicated in the adaptation to stress exposure, cognitive function, and antidepressant response among other relevant CNS functions. It has been found to be decreased (both short and long term) in the hippocampus of animal models of depression. BDNF is reported to promote function, growth, and sprouting of brain 5HT neurons and, for all these reasons, represents an ideal candidate gene for studies of depressive vulnerability. Interestingly, Val-66-Met has been associated with impacting intracellular trafficking and activity-dependent secretion of BDNF, with the "66-Met" form showing less depolarization-induced secretion of BDNF (75). The BDNF dinucleotide G-Tn polymorphism and Val-66-Met single-nucleotide polymorphism were significantly associated with BD in a family-based association study of European-descent probands (76). However, other studies involving Japanese and Chinese populations have failed to find a Val-66-Met association with mood disorders.

Another pathway and gene system that has been associated with MDD is the cAMP response element binding protein 1 (CREB1), the main postsynaptic second messenger signaling system. A linkage finding only in women with recurrent early-onset MDD has been reported for the CREB1 region on chromosome 2q33-35 (77). This extended to a linkage finding in families with recurrent early-onset MDD (78), and polymorphisms in the CREB1 gene were characterized as a sex-specific finding (79). The influence of a promoter polymorphism in the CREB1 gene has been shown to functionally interact with stress hormones in both neuronal (80) and glial cells (81) in vitro, and may explain some of the etiology of MDD in women.

Several very promising candidate gene association efforts are currently ongoing, facilitated by the large clinical sample of MDD cases collected as part of the National Institutes of Mental Health multi-site collaborative study entitled Sequenced Treatment Alternatives to Relieve Depression (STAR*D) (82). A portion of the participants of the trial have been genotyped and subsequently tested for association between genetic variants and disease status or treatment response by several research groups, with much of the research still ongoing. One candidate gene association study has found links to FKBP5, a gene involved in regulating activity of the hypothalamic-pituitary-adrenal axis, with MDD (83). Associations with antidepressant response (84) and BD (85) have also been reported for this gene.

GENETICS AND ANTIDEPRESSANT RESPONSE

The concept of personalized medicine in psychiatry has focused around antidepressant treatment for MDD. Among the genes theoretically likely to contribute to interindividual differences in treatment response are the

drug-metabolizing genes in the cytochrome P (CYP)450 pathway. One STAR*D group investigated association between several pharmacokinetic genes and found no association with response or tolerance to the antidepressant citalopram (86). These findings are consistent with results from an earlier study in which pharmacodynamic genes (e.g., HTR2A, SERT, etc.) were found to play more of a role in predicting tolerability and antidepressant response than pharmacokinetic genes (e.g., CYP2D6, CYP2C19, etc.) (87). Much controversy surrounds the idea of conducting genotyping to inform the decision of agent and dose selection of antidepressants. Although there are many commercially available arrays to test drug metabolism genes, a recent decision from an independent government panel discourages the use of genotyping CYP450 gene to guide antidepressant treatment (88). Genotyping on the serotonin transporter gene (SLC6A4) is also commercially available, however, the inconsistent reports of association in various ethnic groups limit the clinical applicability of this genetic information.

Another potential source of treatment resistance is the presence of defective molecular transport across the blood-brain barrier. P-glycoprotein is a well-known transporter molecule of the ATP-binding cassette (ABC) protein family, which helps to regulate the brain concentration of many antidepressant substrates. Association between several functional allelic variants of the ABCB1 gene and clinical response to antidepressant treatment for major depression has been reported (89). These findings exist only for those treated with antidepressant medication that uses p-glycoprotein as a transporter (such as citalopram and venlafaxine). No association with MDD was found for these variants in the ABCB1 gene.

CONCLUSION

In this chapter we offer a readable, general overview of the rationale and common methodology for the study of genetic effects in MDD. We discussed, among the most relevant findings, evidence that implicates genetic factors in the etiology of depression-related phenotypes. It has long been demonstrated that depression is a familial phenotype and it is broadly accepted that MZ twins share higher concordance rates compared with dizygotic twins, and that reports of heritability estimates for MDD range from 29% to 75% depending on methodological issues. The use of candidate genes and the incorporation of novel etiologically defined quantifiable phenotypes may prove to be an adequate complement to traditional psychiatric genetic approaches. Consistent findings with these methodologies may help clarify the underlying mechanisms required for normal brain function, disease states, or the continuum in specific quantitative traits. Recent findings further support the notion that identifying environmental risk or protective factors and assessing their interaction with genes must become a routine element in psychiatric genetic studies. Recent advances in biotechnology, bioinformatics, and biostatistics, coupled with improved phenotypes, may facilitate progress despite the identified challenges in dealing with complex genetic traits in behavioral phenotypes. We look forward to the newer versions of DSM and International Classification of Diseases (ICD) to initiate a process that would take into account these advances and contribute to the clarification of the etiology of mental disorders such as MDD.

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8 Neuroimaging and Electrophysiology Studies in Major Depressive Disorder

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INTRODUCTION

The search for specific neuroimaging and electrophysiology abnormalities in major depressive disorder (MDD) is driven by a clear unmet clinical need. While first-line antidepressant treatments have response rates (defined as 50% improvement of symptoms) of 50% or more, large numbers of patients still fail to respond to multiple interventions (1). In real-life patients (with comorbid medical and psychiatric illnesses), the rates of remission (defined as resolution of symptoms) tend to be low (25–35%); remission rates become very low (10–20%) for those not improving after two initial treatments (2). Moreover, it takes 6 to 12 weeks to fully evaluate the efficacy of an antidepressant treatment. As each new pharmacotherapy is tried, patients are exposed to additional cost, side effect burden, and the potential for loss of function and suicide.

In the last two decades, the widespread availability of neuroimaging and electrophysiology technology has led to new efforts to apply these techniques in two related goals: (*i*) improving the diagnosis of patients with mood disorders and (*ii*) discriminating between likely treatment responders and nonresponders and identifying those at greater risk for relapse. The first goal is the identification of the underlying pathophysiology associated with a given mood disorder (e.g., major depression, bipolar disorder). This effort aims to improve the accuracy of clinical diagnosis or reveal biologically distinct depressive subtypes with different patterns of clinical response and prognosis. In the past, the utility of selective serotonin reuptake inhibitors (SSRIs) in major depression provided evidence for serotonergic dysregulation in some affective illnesses. Similarly, the discovery of disease-specific functional and/or metabolic changes in certain brain regions would implicate those structures in the process of disease development or recovery. These findings could then guide future diagnostic procedures or even drug development. A second goal is finding objective biological (e.g., neuroimaging, EEG) markers of treatment response, which could potentially allow more targeted and focused clinical interventions. The ability to predict treatment response before or shortly after a new treatment is initiated would translate into significant improvement of our treatment selection process, ultimately resulting in a significant increase in the efficacy of our treatments.

In the following sections, we review studies in MDD involving multiple imaging modalities [structural and functional neuroimaging and magnetic resonance spectroscopy (MRS)], as well as electrophysiology studies. We will

briefly interpret their results, and we will address some of the problems and limitations associated with these approaches.

Original reports or reviews included in this chapter were identified by conducting a MEDLINE search with the terms "neuroimaging," "MRI," "fMRI," "PET," "SPECT," "MRS," and "EEG," combined with either "depression," "major depressive disorder," "bipolar disorder," or "affective illness." References in the publications identified were then reviewed manually to locate additional relevant publications.

IMAGING STUDIES

Morphological and functional imaging studies have identified a number of abnormalities in MDD patients, but these findings are often inconsistent or difficult to replicate, possibly because of the small sample size of most imaging studies. However, taken together, the neuroimaging abnormalities in MDD point to an imbalance in the relative role and activity between the limbic regions that putatively mediate emotional and stress responses (such as the amygdala and the hippocampus) and prefrontal cortical regions that appear to modulate and control emotional expression (such as the posterior orbital cortex and the anterior cingulate gyrus) (3,4). This imbalance is reflected in the morphological and functional imaging studies as well as the MRS studies reviewed below.

Structural Imaging

In a typical protocol, imaging is performed comparing medication-free subjects with MDD with age- and gender-matched healthy volunteers. In some studies, MDD patients then enter pharmacotherapy trials, and outcome measures are ultimately correlated with size of brain structures or presence and extent of lesions such as white matter abnormalities. The neuroanatomical abnormalities reported so far in MDD patients include morphological lesions and reductions in gray matter volume (5).

Structural Changes in Specific Brain Structures Involved in Mood Regulation

One of the best-replicated results is that hippocampus volume is reduced in MDD subjects compared with healthy volunteers (6). The finding is supported by a meta-analysis of 17 magnetic resonance imaging (MRI) studies (7), where only a few did not replicate this result (8,9). Reduced hippocampal volumes in depressed patients have been reported in first-episode and in pediatric patients (10,11), but further reductions in hippocampus size have been associated with the effects of hypercortisolemia and chronic stress as well as with longer duration of untreated depression (6,12), suggesting a progressive negative effect of chronic, untreated depressive illness.

A number of researchers have identified decreased volumes in specific frontal lobe areas in depression (13,14) or familial affective illness (15). Volume reductions in the anterior cingulate gyrus of MDD subjects were also reported (15,16) and were corroborated by postmortem studies showing glial reduction in the corresponding gray matter (17). Individuals with genetic risk factors for depression (such as the short allele of the serotonin transporter, 5-HTTLPR s-allele) exhibit volume reductions in bilateral anterior cingulate cortex (ACC) even before experiencing clinical symptoms of depression (18).

Reduced basal ganglia volumes have also been reported in depressed patients (19). There is more disagreement in the literature on amygdala volumes in MDD, which have been reported to be either decreased (20,21) or increased (22).

Structural Changes in the White Matter Tracts

The imbalance in the activity of the limbic system and the prefrontal cortex described in depression could be attributed in specific cases to abnormal white matter connections between these structures. Magnetic resonance imaging also allows the identification of such white matter abnormalities. Most MRI reports of an increased incidence of brain white matter lesions (WML) have involved elderly MDD subjects compared with age-matched controls (23,24). In younger MDD subjects however the results are still equivocal: some studies reported increased incidence of WML (25), while others did not (26). The presence of brain WML has been associated with cardiovascular risk factors such as age, prior cerebrovascular disease, smoking, arterial hypertension, and increased serum cholesterol (27–29). Neuropathological studies have reported a large proportion of WML in depressed subjects to be related to brain vascular disease (30).

Recognition of the increased prevalence of brain WML in major depression has led investigators to describe "vascular depression," a subtype of MDD characterized by the presence of cerebrovascular disease (demonstrated on neuroimaging by brain WML) (23,31). Compared with MDD subjects with no WML, some studies found that the presence of brain WML in MDD subjects was associated with lower rates of response to antidepressant treatment (32,33), higher rates of irritability and anger attacks (34), history of past suicide attempts (35), as well as higher rates of relapse in long-term follow-up (36). However, other researchers did not find a difference in the outcome of antidepressant therapy in depressed subjects with or without WML (37).

These conflicting results may point toward specific brain regions where the presence of WML has an impact on MDD. Not all WML appear to be equal in the etiology of depression. Several studies appear to conclude that brain WML in the frontal lobes and/or basal ganglia structures are most likely associated with the presence of clinical depression and with poor response to antidepressant treatment (32,33,38).

A modern technique to study the structural integrity of white matter is diffusion tensor imaging (DTI). DTI studies have also highlighted structural abnormalities of white matter in the prefrontal lobes of depressed subjects (39) that are associated with poor response to antidepressant treatment (40).

Overall, structural imaging studies in MDD suggest the presence of volumetric abnormalities in limbic areas that mediate emotional and stress responses (e.g., hippocampus), as well as in brain cortical regions that putatively control and modulate emotional expression (such as the prefrontal cortex and the anterior cingulate gyrus). The presence of WML further disrupts white matter circuits linking the limbic structures with the anterior cingulate and the prefrontal cortex; this may explain the association between WML in specific brain areas and higher prevalence of MDD and poor response to antidepressant treatment.

Functional Imaging

Functional neuroimaging techniques assess changes in brain blood flow or metabolism and allow inferences to be drawn about brain areas that are hyper or

hypoactive in various disease states. Available technologies include single photon emission computed tomography (SPECT), positron emission tomography (PET), and functional MRI (fMRI).

Earlier investigators have simply compared *at rest (baseline)* the blood flow and metabolic rates in MDD subjects and healthy volunteers. PET studies and SPECT studies have shown lower fluorodeoxyglucose metabolic rates and decreased blood flow, respectively, in the frontal lobes of subjects with major depression imaged at rest (41). The most fruitful use of functional imaging studies (fMRI, PET) has been the study of abnormal activation of brain circuits (as measured by changes in blood flow or metabolism patterns) during specific emotional and cognitive tasks. For example, compared with healthy volunteers, MDD subjects had a different pattern of amygdala-increased activation when exposed to anger induction (42), emotional faces (43), or sad words (44).

In MDD subjects, PET studies have demonstrated multiple abnormalities of regional cerebral blood flow (CBF) and glucose metabolism in limbic and prefrontal cortical structures. Relative to healthy controls, regional CBF and metabolism in depressed subjects are increased (hyperactive) in the amygdala, orbitofrontal cortex, and medial thalamus and decreased in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate gyrus. Moreover, these metabolic functional abnormalities appear to improve after antidepressant treatment (45–47).

In the amygdala, during depressive episodes, the resting CBF and glucose metabolism are abnormally elevated, correlating with depression severity consistent with this structure's role in organizing the autonomic, neuroendocrine, and behavioral manifestations of some types of emotional responses (48). These metabolic abnormalities are also associated in depressed subjects with abnormal amygdala CBF responses to emotional stimuli, such as anger induction (42), emotional faces (43), or sad words (44).

CBF and glucose metabolism are also abnormally increased in the orbitofrontal and the ventrolateral prefrontal cortex in unmedicated subjects with MDD; these values tend to normalize after successful treatment (49). Dysfunction of this brain region has also been associated with impaired emotional processing and decreased hedonic response as well as increased stress (50). Inducing negative emotions in MDD subjects reveals an abnormal activation in the orbitofrontal cortex (51).

In contrast, several PET studies of MDD reported abnormally decreased CBF and glucose metabolism in the DLPFC, which normalized after antidepressant treatment (52–54). Inducing negative emotions in MDD subjects reveals hypoactivation of the DLPFC (55). These findings may be explained by the reported abnormal reductions in the density and size of neurons and glia seen in the same brain areas in postmortem studies of MDD (56). Theoretically, hypofrontality may also explain poor concentration, ambivalence, and executive dysfunction seen in MDD as well.

Similarly, CBF and metabolism in the subgenual anterior cingulate gyrus are decreased at rest in depressive subjects compared with healthy volunteers (15,57). This abnormality is also associated with a volumetric reduction of the corresponding cortex, measured by MRI-based morphometry (16) and by postmortem neuropathological studies (17). Of interest, responders to antidepressant treatment appear to show decreased activity in subgenual cingulate gyrus (area 25) and increased activity in specific cortical areas; nonresponders did not show this pattern (58).

Various lines of evidence from these functional studies implicate a specific brain network involved in the control and modulation of emotions. This network includes brain structures such as prefrontal and parietal cortices, anterior cingulate, hippocampus, amygdala, as well as other limbic and paralimbic structures, all important in affective illnesses (59,60). Drevets (53) also postulated a series of interconnected neural circuits in the pathology of MDD. These circuits would include limbic-thalamic-cortical and limbic-cortical-striatal-pallidal-thalamic circuits, involving the amygdala, orbital and medial PFC, and anatomically related parts of the striatum and thalamus. These circuits have also been implicated more generally in emotional behavior by the results of electrophysiological lesion analysis and brain-mapping studies of humans and experimental animals (53). Thus, the symptoms characteristic of mood disorders would not be circumscribed necessarily to only one brain structure, but would represent a relative imbalance in the interaction of different structures participating in the brain network for emotion regulation (61).

Functional imaging studies (fMRI, PET, SPECT) have also been used to study *treatment response* in MDD. The same brain areas involved in mood regulation have also been the locus of metabolic changes as a result of antidepressant treatment in MDD. Earlier studies of treatment response used measures such as global metabolism and left hemisphere to right hemisphere ratios to assess differences before and after treatment. Some authors demonstrated normalization of baseline cerebral hypometabolism after treatment (52,62), while others reported continuous hypometabolism despite clinical response (63,64). Other authors found that prefrontal and paralimbic hypometabolism predicted a positive response to antidepressant treatment (65,66). In contrast, Mayberg et al. (58,59) reported that an increased glucose metabolism rate in the anterior cingulate gyrus predicted treatment response at six weeks, and decreased metabolism in the same region predicted treatment resistance. The finding of such a striking pattern in an area identified in prior studies and known to have important reciprocal connections with other limbic structures was intriguing. More recently, Brody et al. (67) and Saxena et al. (68) have reported that treatment response in MDD correlated with greater decreases in glucose metabolism in the ventrolateral prefrontal cortex from pre- to posttreatment. Mayberg et al. (69) confirmed metabolic changes during antidepressant treatment in MDD and found a specific pattern of activation (in the striatum, anterior insula, and hippocampus) differentiating true antidepressant response from placebo response in MDD. During a cognitive, nonemotional task, MDD subjects had higher activation of amygdala and inferior frontal cortex compared with healthy volunteers; higher activation in these areas was associated with later response to antidepressant treatment (70). However, while these studies are very encouraging, the value of functional neuroimaging studies as predictors of treatment outcome in individual subjects is still to be determined.

SPECT or PET can also be used, with appropriate ligands, to examine the distribution or density of neurotransmitter receptors in vivo and to correlate changes with treatment response. In one such study, Larisch et al. (71) assessed D_2 receptor binding before and after SSRI treatment in 13 MDD subjects. Responders demonstrated increased D_2 receptor binding in striatum and anterior cingulate following treatment, compared with nonresponders.

Overall, the findings of functional neuroimaging studies suggest that MDD is associated with activation of regions that putatively mediate emotional

and stress responses (such as the amygdala), while areas that appear to inhibit emotional expression (such as the prefrontal and orbital cortices) contain morphological and functional abnormalities that might interfere with the modulation of emotional or stress responses (3). This functional imbalance between limbic and cortical structures in MDD may be corrected by successful antidepressant treatment.

Magnetic Resonance Spectroscopy

MRS, a noninvasive tool for in vivo chemical analysis, has also been used to correlate treatment response with brain levels of several neurochemicals. MRS has several important advantages in the study of mood disorders. PET and SPECT allow differentiating between hyper- and hypometabolic tissue by measuring blood flow or FDG glucose metabolic rate; however, no information can be obtained. But no information can be obtained about specific metabolic pathways involved. In contrast, MRS allows measuring the concentration of a large number of metabolites (72). Therefore, one can measure chemical abnormalities and the effect of medications on different metabolic pathways. Moreover, MRS permits the study of several brain chemicals without the introduction of exogenous tracers or exposure to ionizing radiation.

Most commonly, MRS studies in psychiatric disorders involve proton (1H) and phosphorus (P^{31}) spectroscopy. Such protocols have been developed to enable the measurement of brain neurotransmitters (GABA, glutamate) and structural components of cells (synaptic proteins, membrane phospholipids) (73). Less often, MRS is also used to measure brain levels of psychotropic drugs including lithium and fluorinated drugs such as SSRIs, and correlating such levels with observed clinical response. Lithium-7 MRS has been utilized to demonstrate the variability in brain lithium levels among bipolar patients during maintenance therapy despite similar serum levels (74). Similarly, fluorine-19 MRS measurement of brain paroxetine levels showed a correlation between withdrawal-emergent side effects and paroxetine brain levels (75). Whether these levels would be useful in predicting clinical response, however, is unknown; one open trial of fluvoxamine in obsessive-compulsive disorder could not assess the predictive value of fluorine-19 MRS because seven of eight subjects responded (76).

Proton (1H) MRS Studies of Patients with MDD

Proton magnetic resonance spectroscopy (1H-MRS) may be useful in identifying MDD-specific differences in the chemical composition of brain structures and correlations between such abnormalities and antidepressant treatment response (ATR). Studies utilizing 1H-MRS in MDD have generally focused on changes in cerebral concentrations of creatine (Cre), *N*-acetyl aspartate (NAA), cytosolic choline (Cho), myoinositol (MI), γ-aminobutyric acid (GABA), and glutamate.

Significant deficits in MDD subjects have been identified in the cellular membrane phospholipid metabolism, as measured by Cho levels in the orbitofrontal cortex (77). Proton MRS studies have documented both increases (78,79) and decreases (80) in the intensity of the 1H-MRS Cho resonance in depressed populations. Variation in reported results may reflect differences in study methodology and in the brain region investigated. In a meta-analysis of 15 studies (240 patients and 261 controls), Yildiz-Yesiloglu and Ankerst (81)

reported that Cho values were higher in the basal ganglia of adult MDD subjects. Moreover, baseline estimates of Cho signal intensity, as well as change with treatment, have been shown to correlate with clinical response (80). In a subsequent publication, the authors also reported that change in Cho levels correlated with "true" drug response, compared with "placebo-pattern" response or nonresponse, in MDD patients (82). Ende et al. (83) also report a significant increase in hippocampal Cho after electroconvulsive therapy (ECT). As Cho is a precursor in phospholipid metabolism as well as synthesis of acetylcholine, it may indicate metabolic differences associated with response to antidepressant treatment.

1H-MRS was also used to identify abnormalities in neurotransmitter levels in patients with MDD. Sanacora and coworkers (84–88) have reported dramatic reductions in occipital cortex GABA levels (greater than 50% reduction) in unmedicated MDD subjects compared with healthy volunteers. Moreover, two separate studies reported significant increases in GABA levels in the occipital cortex of MDD subjects after treatment with SSRIs (86) and after ECT (87). Since most subjects had improved with antidepressant treatment, there was no statistically significant correlation in these small studies between brain GABA levels and ATR. More recently, prefrontal GABA levels were also found to be reduced in the frontal lobe (89). These results are consistent with reports of decreased GABA function and decreased $GABA_A$ receptor binding in animal models of depression (85) and with earlier reports of decreased GABA levels in the cerebrospinal fluid of MDD patients compared with normal controls (90). SSRIs are known to induce increases in brain allopregnenolone (91), a neurosteroid with high affinity for $GABA_A$ receptors, which facilitates GABAergic actions. This is the mechanism by which Ketter and Wang (92) explain the SSRI role in increasing brain GABA levels.

A majority of studies suggest that glutamate levels are decreased in MDD. Most studies reported a common peak (Glx) representing combined levels of glutamate and glutamine. Several researchers reported decreased Glx levels in the frontal lobe of MDD subjects (81,93,94), while Glx levels were increased in the occipital lobe (88). More recent studies have reported reduced Glx in the frontal lobe of MDD subjects (89). Therefore, a majority of studies appear to suggest that frontal lobe glutamate levels are low in MDD, in contrast with bipolar disorder. Abnormal brain glutamate levels in MDD would be consistent with animal and postmortem studies on the role of glutamate and of *N*-methyl-D-aspartate receptors in MDD (95). The reductions in glutamate and GABA are compatible with postmortem studies indicating reduced glial density in the prefrontal areas in MDD (56).

Decreased myoinositol levels in the right frontal lobe were also found in MDD subjects relative to healthy volunteers (96,97). Since the myoinositol resonance reflects the concentration of cellular phosphatidylinositol, an important component of cellular second messenger system, this finding suggests an abnormality of second messenger systems may be present in MDD.

P^{31}-MRS Studies of Energy Metabolism in MDD

Phosphorus magnetic resonance spectroscopy (P^{31}-MRS) is used to noninvasively determine cerebral levels of high-energy phosphates such as phosphocreatine (PCr), β-nucleoside triphosphate (β-NTP), which in the brain

represents mostly ATP, and total NTP, as well as phosphomonoesters (PMEs) and phosphodiesters (PDEs), which are involved in brain phospholipid metabolism. Abnormalities of brain energy metabolism have been reported in MDD subjects: decreased β-NTP levels in basal ganglia (98,99) and frontal lobes (100). PCr, which has a buffer role for ATP, was increased in MDD subjects (101,102). Since NTP primarily reflects levels of intracellular ATP, decreased NTP signifies a reduction of cellular bioenergetic metabolism. Reduced cellular ATP levels would also be consistent with previous observations of alterations in the brain phospholipid metabolism (high Cho levels); both are suggestive of an underlying mitochondrial dysfunction. The levels of bioenergetic metabolism appear to also be correlated with response to antidepressant treatment. At baseline, β-NTP was lower (99) and PCr was higher (101,102) in MDD subjects who responded to antidepressant treatment, compared with nonresponders. Baseline PCr appeared potentially useful as a predictor of antidepressant response (83% sensitivity and 75% specificity). During the antidepressant treatment, total NTP and β-NTP increased in treatment responders, while PCr showed a compensatory decrease; neither change was present in treatment nonresponders (101,102).

Phospholipid (PMEs and PDEs) levels were also reported to be increased in MDD (100). As membrane anabolites, in normal cellular function, PMEs are incorporated into the phospholipid membrane at the expense of ATP (103). Consequently, increased PME in MDD patients may reflect increased breakdown and turnover of cellular membrane, which in turn might be related to decreased availability of ATP. Additionally, these findings suggest that in MDD subjects, alterations in both phospholipid metabolism and mitochondrial function may be closely related to mood state. The majority of these findings can be fit into a more cohesive bioenergetic and neurochemical model that is focused on central nervous system (CNS) energy metabolism (104). These findings suggest a model of mitochondrial dysfunction in MDD that involves a shift toward glycolytic energy production, a decrease in total energy production and/or substrate availability, and altered phospholipid metabolism. Specifically, a shift toward glycolytic production of ATP may be related to additional MRS findings of reduced concentrations of high-energy compounds in MDD subjects.

Overall, MRS studies have suggested that multiple metabolic and neurotransmitter abnormalities are present in MDD. Understanding of the relationship between these in vivo chemical abnormalities and MDD symptoms may help shed light on the pathophysiology of major depression. These chemical abnormalities may also represent useful targets for predicting treatment outcome in MDD.

ELECTROPHYSIOLOGY STUDIES

Electroencephalography (EEG) is an established technique used to investigate CNS activity. Most depressed subjects have visually normal EEG tracings (105). Most significant EEG abnormalities in MDD subjects have been associated with underlying comorbid pathology, such as cerebrovascular disease or early dementia (106). A more modern version is quantitative EEG (QEEG) in which a digitized signal on magnetic or optical media replaces paper tracings. QEEG involves computerized spectral analysis of EEG signals, providing information that cannot be extracted through visual inspection of EEG.

No EEG measures are entirely specific to MDD. Cordance, a QEEG measure integrating absolute and relative power of the signal, was shown to be decreased in subjects with MDD, compared with normal subjects (107). However, cordance is lowered both by advanced age, by delirium, or dementia, and is therefore not specific to MDD. Presently no EEG-derived measure can reliably assist in the diagnosis of MDD.

However, multiple studies have suggested that QEEG measures might be useful predictors of the outcome of antidepressant treatment in MDD. Most of the earlier studies are hard to compare, as they differ with regards to the EEG features examined, time points of examinations, EEG electrode montages, and the analytical methods utilized. A number of pretreatment EEG variables were reported to differentiate between responders and nonresponders to tricyclic antidepressants (TCAs), especially in the alpha (108) and theta bands (109). Lateralized alpha power was also associated with response to fluoxetine (110).

Cordance, a QEEG measure that integrates the absolute and relative power of the EEG signal, was found to predict clinical response in 51 subjects treated with fluoxetine or venlafaxine (111). Using prefrontal theta cordance at week 1 as a predictor of clinical response (measured at week 8) led to an accuracy of 72% (sensitivity 69%, specificity 75%). Given that this previous study indicates prefrontal EEG leads are primarily responsible for response prediction, our group recently used a simple four-channel EEG to investigate prefrontal theta power as a predictor of treatment response to SSRI antidepressants. This variable provided 67% prediction accuracy (71% sensitivity, 61% specificity). We retrospectively defined a three-parameter ATR index, which combines EEG parameters recorded at baseline and week 1. The ATR index provided 76% prediction accuracy (81% sensitivity, 72% specificity) (112). Recently, preliminary results have been presented from the large multicenter study Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression (BRITE-MD). BRITE-MD tested prospectively the predictive ability of the ATR index in 220 MDD subjects who started treatment with escitalopram and one week later were randomized to either continue to escitalopram, switch to bupropion, or augment with bupropion (113). In this study, ATR had a 74% accuracy in predicting both response and remission.

Other researchers have used EEG to predict response to ECT. The emphasis in such studies has been on the analysis of the ictal EEG to discriminate "effective" from "ineffective" seizures (114). However, most studies also attempted to assess baseline EEG features that were predictive of subsequent response. For example, fractal analysis of EEG data from the initial induced seizure was significantly associated in one study with remission status at two weeks among 40 MDD patients receiving bilateral ECT (115). This result is consistent with earlier findings suggesting predictive value for postictal suppression (116). However, other studies have not supported the usefulness of QEEG analysis to predict response to ECT (117).

Low-resolution electromagnetic tomography (LORETA), in which QEEG data was used to create three-dimensional maps of cortical currents and to localize the sources of electrical impulses, has also been used to investigate brain electrical activity in MDD. Pizzagalli et al. (118) reported that theta activity in the rostral anterior cingulated gyrus in MDD subjects was directly correlated with treatment improvement (measured with BDI).

Event-related potentials (ERP) measure voltage changes on the scalp surface that correspond to cortical or brainstem activity in response to sensory stimuli. One such technique is the loudness-dependence of the auditory evoked potential (LDAEP)—which describes how one ERP component (N1/P2) changes with increasing loudness of the auditory stimulus. The LDAEP is believed to correspond to the magnitude of serotonergic neurotransmission in auditory cortex, particularly primary auditory cortex (119). Several investigators have reported an association between LDAEP and antidepressant response with SSRIs (120–122) or bupropion (123).

Other studies suggest that baseline QEEG parameters may also serve to predict the total burden of treatment-emergent side effects (124) or more specifically to predict treatment-emergent suicidal ideation (102).

Overall, EEG abnormalities are not specific to MDD, but computerized analysis of EEG signals appears to detect patterns of activity associated with response to antidepressant treatment.

CONCLUSION

In conclusion, neuroimaging and electrophysiology studies in MDD reveal multiple brain abnormalities at anatomical, metabolical, and functional levels. But while the results summarized above represent a significant progress in understanding brain function in depression, no biological measure has yet shown clear clinical utility. Research findings have been suggestive but not yet conclusive. Results with functional neuroimaging techniques and MRS may be particularly promising in detecting the brain neurocircuits involved in emotion regulation as well as metabolic abnormalities in MDD. Different forms of QEEG show promise as predictors of treatment response, which might eventually allow clinicians to select among antidepressant treatments based on objective predictors of success. But future studies will be necessary to clarify the generalizability of the current findings and to validate (or not) their usefulness for clinical practice and for our understanding of the pathophysiology of MDD.

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9 Advances in Neurostimulation for Depression: Electroconvulsive Therapy, Transcranial Magnetic Stimulation, Vagus Nerve Stimulation, and Deep Brain Stimulation

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OVERVIEW

Major depression is a common and debilitating disorder. It has been estimated that half of depressed patients treated with standard antidepressant medications do not show evidence of adequate response (1). A recent large multicenter clinical trial examined the effectiveness of serial antidepressant treatment interventions in ($n = 3671$) depressed outpatients [STAR*D (sequenced treatment alternatives to relieve depression)] (2). Through a stepwise progression through multiple, serially administered, adequate antidepressant treatment trials, this trial demonstrated a cumulative remission rate of only 67% (3). Non-pharmacological neurostimulation therapies may offer additional options for depressed patients who have failed to respond to standard psychotherapy and pharmacological therapies.

Electroconvulsive therapy (ECT) is the oldest and most widely used neurostimulation technique for depression. Vagus nerve stimulation (VNS) was approved by the U.S. Food and Drug Administration (FDA) in 2005 as an adjunctive treatment for treatment-resistant major depression, and a device for the delivery of transcranial magnetic stimulation (TMS) therapy for depression was approved by the FDA in late 2008. Deep brain stimulation (DBS) has shown promise in preliminary, pilot studies of treatment-resistant depression, and large controlled trials are now underway. This chapter will review each of these neurostimulation techniques in detail and discuss the state of the evidence base for these somatic therapies.

ELECTROCONVULSIVE THERAPY

ECT has been in use since the 1930s, and is still widely considered the most effective treatment for severe forms of depression. In addition to being considered the "gold standard" with regard to efficacy for treatment of severe melancholic or psychotic depression, ECT has been used to treat various other severe psychiatric disorders, including mania, schizophrenia, and catatonic states (4).

ECT involves the unilateral or bilateral application of a brief electrical impulse directly to the scalp to induce seizures. There is a general consensus that the ECT stimulus must produce a tonic-clonic seizure movement pattern in addition to a characteristic tracing on a scalp electroencephalograph recording for at least 20 seconds to produce a therapeutic effect (5). Patients receive general anesthesia during modern ECT, and anesthesia-induced muscle relaxation prevents generalized convulsive body movements during the course of each ECT session. A typical acute course of ECT consists of between 6 and 12 treatments at a frequency of 2 to 3 treatments per week, and some patients require maintenance treatment consisting of weekly or monthly treatments. ECT is generally administered by a specially trained psychiatrist in an inpatient or outpatient hospital setting.

Two recent meta-analyses, incorporating data from both controlled and observational studies, confirmed the efficacy of ECT for depressive disorders (6,7). In the first, ECT was more effective than sham treatment in an analysis of six trials ($n = 256$), as evidenced by a standardized effect size (SES) of -0.91 [95% confidence interval (CI) -1.27 to -0.54] (7). Analysis of data from 18 trials ($n = 1144$) suggested that ECT was significantly more effective than pharmacotherapy (SES -0.80, 95% CI, -1.29 to -0.29) (7). Bilateral ECT was proven superior in efficacy to unipolar ECT (22 trials, $n = 1408$; SES -0.32, 95% CI, -0.46 to -0.19) (7). The second meta-analysis, which included data from both randomized and nonrandomized controlled trials published from 1956 to 2003, also confirmed the superiority of ECT in comparisons with simulated (sham) ECT, placebo, antidepressants in general, tricyclic antidepressants, and monoamine oxidase inhibitors (6).

Sackeim et al. reported that the clinical efficacy of ECT depends on electrode placement (i.e., bilateral treatment is superior to unilateral) and stimulus intensity as a function of an individual's seizure threshold (i.e., higher doses superior to lower doses) (8), while the absolute electrical dose is unrelated to clinical efficacy. A relatively high dose (relative to seizure threshold) and bilateral electrode placement appear to be most effective for alleviating depressive symptoms, although these parameters are associated with greater impairment of short-term cognitive function. This relationship is particularly notable in the elderly population receiving bifrontal ECT (9). While low-dose, right-sided unilateral ECT is considered the least effective method of delivery (8), further refinement of right-sided unilateral stimulation parameters, specifically the use of a stimulus pulse width of 0.1 to 0.3 milliseconds and an electrical dose that adequately exceeds the seizure threshold, can produce a response equivalent to that achieved with standard bilateral ECT (10).

Published efficacy data from ECT research protocols are impressive (response rates in the 70–90% range), but analyses of treatment in community settings have revealed significantly lower remission rates, from 30% to 47%, depending on the specific remission criteria applied (11). In a naturalistic six-month follow-up study, comorbid personality disorders, depressive episode chronicity, and schizoaffective disorder were associated with poorer outcomes (11). Among those who did achieve remission in that study, 64% relapsed during follow-up despite maintenance ECT or pharmacotherapy.

Sustaining antidepressant benefits achieved with ECT remains a significant challenge. Relapse rates have been observed to be as high as 84% within six months of initial ECT treatment in the absence of continued treatment, but the relapse rate can be reduced by the use of optimal antidepressant

pharmacotherapy (12). Naturalistic data provide additional support for the notion that a combination of maintenance ECT plus antidepressant medication is superior to medication alone for preventing relapse (13). A multicenter, randomized, six-month trial that compared continuation ECT with pharmacotherapy following ECT-induced remission showed no significant difference between the two treatments in relapse prevention, with both treatment arms generating relapse rates >30% (14). A naturalistic study examining follow-up outcomes four to eight years after ECT in 26 patients found an overall recurrence rate (i.e., a new episode requiring treatment) of 42.3%, and determined that future recurrence was not associated with clinical outcome in the six months immediately following the initial ECT treatment (15).

Despite the robust efficacy data associated with ECT, many factors other than the high relapse rate limit the use of ECT. Patient access is limited because of the required hospital setting, high cost, exposure to anesthesia, and risk of side effects, most notably cognitive side effects (8). Immediate post-ECT side effects include short-term memory loss and cognitive impairment, specifically with impaired selective attention and executive function (16,17). The extent and duration of longer-term cognitive side effects appear highly variable, and various aspects of ECT treatment may have a potential effect on cognition (18).

Anterograde memory deficits have been shown to significantly improve within one week of the ECT procedure, and the administration of pulse-wave ECT appears to have less effects on attention and executive function than sine-wave ECT (17). Several studies have evaluated the prominence of ECT-induced short-term memory loss and cognitive impairment over time and found persistent or residual effects to be minimal. One research group found that baseline memory function returned to the level measured at (depressed) baseline one month after brief-pulse ECT and showed a substantial improvement in memory function relative to depressed baseline at a six-month follow-up (19). Another recent report of six-month outcomes concluded that three ECT sessions produced superior clinical benefits over standard pharmacotherapy, including improvement in overall memory function relative to that at depressed baseline, especially when clinical benefits were marked (20). A small naturalistic follow-up study of 10 ECT patients found evidence of slightly subnormal performance on working memory and verbal and visual episodic memory tasks over two years, but found no severe persistent side effects of ECT or clinically significant signs of a residual mood disorder (21).

In contrast, results of a large-scale, multicenter, prospective study examining the cognitive effects of ECT were recently published (18), demonstrating a link between persistent retrograde amnesia and bilateral ECT. In addition, sine-wave stimulation was associated with a pronounced slowing of reaction time, both immediately and in the six months following ECT. Advancing age, lower premorbid intellectual function, and female gender were found to be associated with greater cognitive deficits (18). These data underscore the need for safer and more tolerable neurostimulation therapies for severe depressive syndromes.

TRANSCRANIAL MAGNETIC STIMULATION

The basic physical principle underlying TMS dates back to the work of Michael Faraday, who in 1839 discovered that a magnetic field can produce an electrical current in a conductive substance, later described as the principle of

electromagnetism (22). In 1985, Barker and Cain (23) developed the first TMS device that was capable of stimulating the human cortex, although at that time their initial goal was stimulation of spinal roots rather than stimulation of the brain. Shortly thereafter TMS was postulated as a possible treatment for depression (24). After more than two decades of research on TMS, a device for treatment of depression was approved by FDA in late 2008.

During TMS, a small, insulated electromagnetic coil is placed on the scalp. A bank of capacitors is then rapidly discharged into the coil, which converts the electrical activity into a pulsed magnetic field that then passes through the cranium with minimal impedance, unlike ECT, where much electrical charge is dispersed by bone. The magnetic field induces an electrical field in the underlying cerebral cortex on the basis of the countercurrent principle (25,26). Upon delivery of sufficiently intense TMS to the targeted area, the cortical neurons depolarize and action potentials are generated, likely increasing neuronal activity in the dorsolateral prefrontal cortex (DLPFC). The current technology generates a magnetic field of approximately 1.5 T (comparable to that of a standard MRI), which penetrates to approximately 3 cm beneath the coil surface (27). The pulsing frequency of the field and the excitatory or inhibitory function of the activated underlying neurons determine the ultimate effects on neural circuitry. In general terms, TMS at frequencies of $\leq$1 Hz (slow TMS) is inhibitory and at frequencies $>$1 Hz (fast TMS) is excitatory (28–30). The pulses administered can be single, paired, or in a series (also called a "train"). When TMS is delivered in a series of pulses, this is termed "repetitive TMS" (often abbreviated rTMS). Single- and paired-pulse TMSs are more frequently used for neurodiagnostic purposes, whereas repetitive TMS is believed to have therapeutic potential in psychiatric disorders. (TMS is used in a generic sense, to refer to repetitive trains of therapeutic stimulation, throughout this chapter.) Unlike ECT, which produces a widespread current distribution via a generalized seizure, the TMS device is able to induce currents in fairly specific, localized area (31).

Before using TMS to deliver therapy, the amount of energy required is determined by calibrating the TMS device via stimulation of the motor cortex. The amount of energy needed from the TMS device is varied until a visible twitching movement ("motor threshold," MT) of the contralateral thumb is reliably produced following single pulses of TMS. In the treatment of depression, determination of the MT on the left motor cortex guides the dosing for the power of treatment delivered. TMS therapy dose is described as the percentage of MT, which for most patients is in the 80% to 120% range. The point of the optimal derived MT on the scalp subsequently guides the anatomical placement of the magnet coil for TMS treatment. For example, to deliver TMS targeting the left DLPFC, the coil is moved 5 cm anteriorly in a parasaggital plane, relative to the spot where the MT was elicited.

There are a variety of treatment variables for TMS, including the inter-train interval (the time in between trains of stimulation when no stimulation is occurring, which is an important safety parameter used to avoid inducing seizures), frequency of pulsing of the magnetic field (expressed in hertz), number of trains per session, and the duration of the session. Generally, only a single session is conducted per treatment day, with five sessions per treatment week given for acute treatment. The duration of treatment has varied across published clinical TMS trials. In early studies, the total number of treatment

sessions was approximately 10 to 20 delivered over three to four weeks (32), but more recent research in this area describes an acute treatment phase duration of six or more weeks (33,34). Both right- and left-sided cortical regions have been investigated as therapeutic targets in TMS research.

Similar to other available neurostimulation treatments in psychiatry, the biological mechanism of action of TMS is not specifically known. However, TMS has demonstrated effects in animal models that act as standard assays for antidepressant efficacy. For example, daily TMS reduces immobility in rats during the forced-swim test, a model of learned helplessness and depression (35–37). Additionally, preclinical rat TMS studies have reported that forebrain serotonin output is enhanced and that serotonin receptor function is modulated (38,39). In human studies, functional MRI imaging of 1 Hz TMS over the left DLPFC produced activation of deeper structures, including the insula, putamen, hippocampus, and thalamus, via frontal-subcortical neuronal circuits (40). Clinical neuroendocrine correlates of successful TMS include increased concentrations of thyroid-stimulating hormone (41) and "normalization" of cortisol secretion as measured by the dexamethasone suppression test (42). Additional reports have identified TMS increasing striatal dopamine (43) and increasing plasma levels of brain-derived neurotrophic factor (BDNF), which has been implicated in antidepressant response (44). Patients responding to TMS have also been found to be resistant to rapid tryptophan depletion, a marker of antidepressant effect (45).

Although TMS was first suggested as a possible treatment for depression in 1987 (24) and initial case reports were favorable (46,47), it was nearly 10 years before TMS was first systematically examined as a treatment for depression (48). In a sample of patients with treatment-resistant psychotic depression ($n = 17$), five days of TMS at 10 Hz was administered to different sites on the scalp in a double-blind, sequential crossover design. The left DLPFC stimulation site yielded the best therapeutic effects; after five days of stimulation, researchers reported a 65% response rate that was maintained for the subsequent two weeks (49). Following this, the majority of studies that found TMS efficacy used the left DLPFC.

Klein et al. was the first group to demonstrate in well-controlled trial that slow-frequency TMS at 1 Hz on the right prefrontal areas could also have antidepressant properties (50), which suggested an additional flexibility of TMS. As such, benefits derived from different hemisphere targets and with opposing TMS pulse frequencies suggest that a variety of stimulation parameters may ultimately be used to customize the treatment for individuals with depressive symptoms.

Over the last 10 years there have been at least 40 controlled trials of TMS in depression as a monotherapy or adjunct treatment, for both bipolar and unipolar depressed patients. Results have been mixed with regard to efficacy. An analysis of treatment parameters associated with optimal TMS outcomes in patients with depression revealed that generally longer courses ($\geq$10 days), higher-intensity MTs (100–110% of MT), and a greater number of pulses (1200–1600 per day) yield superior results (51). Whereas TMS response rates of 30% were observed in earlier studies that used suboptimal dosing parameters (51,52), higher rates have been reported by studies using optimized dosing parameters noted above (53).

The results of a large, randomized, double-blind, multicenter study of TMS monotherapy of 325 medication-free patients with major depression were

recently published (34). In this industry-sponsored trial, TMS was delivered five times per week for four to six weeks at 10 pulses/sec, 120% of MT, 3000 pulses/session. All patients met diagnostic criteria for major depressive disorder (MDD) and were minimally to moderately treatment resistant, having failed to respond to at least one but no more than four antidepressant trials during the current depressive episode. In the evaluable sample ($n = 301$), active TMS was superior to sham on the primary outcome measure at week 4, and on the secondary outcome measure at weeks 4 and 6. The initial blinded phase of this study resulted in a 24.5% response rate for TMS compared with 13.7% for sham (34). The effect size of TMS treatment in this blinded phase was similar to currently available antidepressants (0.55 and 0.49, respectively) (27).

At the end of this acute phase portion of the trial, patients who did not respond to stimulation were invited to cross over to an open-label TMS trial with a similarly designed six-week period. Patients remained blinded to their original treatment to generate data for comparing acute TMS responders (i.e., patients originally assigned to sham stimulation) with late responders (i.e., those initially assigned to active treatment who did not respond). A third phase of the study allowed for the transition of TMS into a 24-week continuation phase, with antidepressants available for optional pharmacotherapy if symptoms worsened. Results from the crossover and continuation phases of this trial found that the outcomes for those who crossed to the open-label study were comparable to those observed in the blinded acute phase (42–43% response and 20–27% remission rates) (54). Maintenance of the beneficial effects of TMS was suggested from the 24-week data showing lower relapse rates among those who received active rather than sham treatment (8% vs. 15% relapse rates, respectively) (54). In a subsequent analysis of data from this clinical trial, shorter duration of current depressive episode, lack of comorbid anxiety, and less severe treatment resistance (as measured by number of past failed adequate antidepressant trials) predicted superior antidepressant response to TMS (55). Ultimately, data describing outcomes for a subset ($n = 164$) of this larger clinical trial were submitted to the FDA, resulting in approval of the Neuronetics' device for TMS therapy for treatment of MDD in adult patients who have failed to achieve satisfactory improvement from one prior medication at or above the minimum effective dose and duration in the current episode. For this smaller clinical study population, separation of active TMS from sham on the primary efficacy measure was highly significant at four weeks ($p = 0.0006$).

Researchers continue to explore ways to enhance the efficacy of TMS for depression. Fitzgerald et al. investigated the combined application of fast TMS over the left DLPFC and slow TMS over the right DLPFC in a sample of treatment-resistant patients ($n = 50$) (33). Slow TMS on the right was followed by fast TMS on the left (a sequenced, combination approach) versus a sham condition with similar duration of stimulation on both the right and left sides. Those who received active TMS over a period of up to six weeks had a 44% response rate and a 36% remission rate in their depression symptoms. In another investigation of multimodal TMS, high-frequency stimulation (20 Hz) to the left PFC and low-frequency stimulation (1 Hz) to the right PFC resulted in significantly greater improvements in depressive symptoms compared with sham controls (56). Most recently, the same group investigated the use of "priming" or using brief 6-Hz stimulation before low-frequency TMS treatment for treatment-resistant

depression. Low-intensity, high-frequency priming stimulation appeared to enhance the response to low-frequency, right-sided TMS treatment in a four-week, double-blind, sham-controlled study (57).

The literature presents conflicting evidence on the antidepressant efficacy of TMS versus ECT. At least two studies (58,59) have found TMS to be inferior to ECT, while others have shown them to be comparable. For example, one study reported low response and remission rates for both TMS (50% and 10%, respectively) and ECT (40% and 20%, respectively) in a medication-free, non-psychotic sample of patients with refractory depression (60). In another study, a sample of medication-free, depressed patients ($n = 40$) was randomly assigned to receive 20 sessions of TMS or a course of ECT, and ECT was shown to be significantly more effective than TMS, particularly among the subgroup of psychotic depressed patients (61). Analyses limited to nonpsychotic patients showed similar response rates for the two treatments (55% with TMS and 60% with ECT) (62). Relapse rates six months after TMS did not differ from those observed for ECT at six months in a study where both groups transitioned to maintenance antidepressant medication (63). More studies will be needed to evaluate the relative efficacy of TMS and ECT and to optimally position TMS in a treatment algorithm for depression.

In general, TMS is safe and well tolerated. Common side effects from the Neuronetics' clinical trial, such as application site pain, muscle twitching, toothache, and discomfort in the facial/eye area, generally were mild to moderate and rapidly accommodated by patients. The most significant risk associated with the therapy is inadvertent seizure induction. Remaining within the recommended stimulation parameters, however, confers a margin of safety that should be combined with careful screening for underlying organic brain disease (64). Overall, the risk of an unwanted seizure appears to be <1 per 1000 TMS sessions, and compares favorably to the risk of seizures with marketed antidepressant drugs such as bupropion and tricyclic antidepressants. A recent review found no incidences of seizures in over 10,000 cumulative TMS treatments in 325 patients (65). The administration of a self-reported safety questionnaire (TMS Adult Safety Screen or TASS) is an easily usable screening tool to identify patients at risk before receiving TMS (66). Because the TMS device emits clicking sounds with each train of magnetic pulses, there is the potential for adverse effects on hearing, and mild but generally transient and clinically insignificant shifts in auditory thresholds have occurred (67,68). To minimize auditory risks, patients often wear earplugs during the procedure. Induction of mania is not a widely recognized side effect of TMS, but case reports of switching into mania have been described (69). Improvements in neuropsychological functioning have been reported following TMS administration for depression, but it has not proved possible to clearly separate this effect from the observed improvements in neurovegetative symptoms of depression during recovery from a depressive episode (70).

TMS is noninvasive, does not require anesthesia or surgery, and can be performed on an outpatient basis. Patients are not sedated during the TMS treatment and can usually leave immediately afterward without a recovery period. Overall, because of its ease of use, favorable tolerability profile (71), and benign cognitive profile (70), TMS offers a potential viable alternative for patients who are unable to tolerate antidepressant treatment or who would otherwise have no treatment option besides ECT.

VAGUS NERVE STIMULATION

VNS was approved by the FDA for the treatment of pharmacoresistant epilepsy in 1997. Mood elevations observed in seizure patients initially prompted the investigation of VNS as a treatment for depression (72–75). Clinical trials were conducted, and subsequent data (reviewed below) resulted in the FDA approval of VNS as an adjunct therapy for treatment-resistant depression in July 2005. VNS therapy consists of repetitive, cyclical electrical stimulation applied to the vagus nerve (cranial nerve X) in the left cervical region, by a surgically implanted device that looks similar to a cardiac pacemaker.

In addition to observed mood-elevating effects of VNS in patients with epilepsy, the rationale for investigating VNS as a possible treatment for depression is based on preclinical investigation of VNS in animal models demonstrating the direct effects of VNS on central cortical function, and on human neuroimaging data demonstrating that VNS affects the function of various important limbic structures. Furthermore, the demonstrated efficacy of anticonvulsant medications as mood stabilizers in mood disorders (76–78) provides an additional link between the two therapeutic areas. Investigations in both animals and humans show that VNS alters concentrations of neurotransmitters implicated in mood disorders [i.e., serotonin, norepinephrine, γ-aminobutyric acid (GABA), and glutamate] within the central nervous system (CNS) (reviewed in detail below). VNS is thought to improve mood via ascending projections through the nucleus tractus solitarius to the parabrachial nucleus and the locus coeruleus (79). This is the site of many norepinephrine-containing neurons that have important connections to the amygdala, hypothalamus, insula, thalamus, orbitofrontal cortex, and other limbic regions linked to mood and anxiety regulation (80).

In 1938, Bailey and Bremer (81) described the synchronized activity of the orbital cortex produced by VNS in cats in one of the first published reports, suggesting that VNS directly affected central function. Dell and Olson also noted slow-wave response in anterior rhinal sulcus and amygdala to VNS in awake cats with high cervical spinal section (82). Primate studies provided further evidence of VNS effects on basal limbic structures, thalamus, and cingulate (83). On the basis of these findings, Zabara hypothesized and further investigated in dogs that VNS would have anticonvulsant action (84,85). Zabara, using standard electrical engineering principles, postulated that the antiepileptic mechanisms of action of VNS would involve both direct termination of an ongoing seizure as well as seizure prevention when he observed VNS-induced cortical electroencephalogram changes and seizure cessation in dogs (86).

The effects of VNS on the brain have been studied using a variety of neuroimaging techniques, such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) (87–89). Garnett et al. (90) showed using PET that left VNS in epilepsy caused increased regional cerebral blood flow (rCBF) in the ipsilateral anterior thalamus and the cingulate gyrus. Ko et al. (91) found increased blood flow in the contralateral thalamus and posterior temporal cortex, and ipsilateral putamen and inferior cerebellum with left VNS. Henry et al. studied both acute and chronic effects of VNS on the brain (92–95). High-level (500 microseconds, 30 Hz, 30 seconds on, 5 minutes off, mean 0.5 mA) left-sided VNS increased the blood flow to the rostral and dorsal medulla oblongata as well as bilateral orbitofrontal gyri, right entorhinal cortex, and right temporal

pole, whereas both high- and low-level (130 microseconds, 1 Hz, 30 seconds on, 180 minutes off, mean 0.85 mA) stimulation increased the blood flow to the right thalamus, right postcentral gyrus, bilateral inferior cerebellum, as well as bilateral hypothalamus and anterior insula. VNS also decreased blood flow to the bilateral amygdala, hippocampus, and posterior cingulate gyrus (92–94). Conway et al. reported acute VNS-induced rCBF changes consistent with brain structures associated with depression and the afferent pathways of the vagus nerve (88). Chronic VNS as adjunctive therapy produced protracted and robust declines in resting brain activity in ventromedial prefrontal cortex, a network with dense connectivity to the amygdala and structures monitoring the internal milieu (95).

Various SPECT studies (96–98) have demonstrated decreased thalamic activity, possibly reflecting the chronic changes in the brain or the acute "off" effect of VNS since SPECT was performed immediately after VNS was turned off or during the period when VNS was mostly off (87). Devous (99) demonstrated in six depressed patients receiving VNS in an open-label study that the patients had reduced rCBF to the left dorsolateral prefrontal, anterolateral temporal, and perisylvian temporal structures, including posterior insula. Zobel et al. (100) reported rCBF changes in multiple limbic structures following four weeks of VNS in 12 patients with TRD. Decreased activity in cingulate gyrus, an area implicated in the pathoetiology of depression, has been associated with symptom relief in various studies (101–103). Therefore, modulation of activity in the cingulate gyrus by VNS, along with VNS effects on the activities of the brain stem, limbic system, and other CNS areas, implicates a similar mechanism for VNS antidepressant activity (104).

Both clinical and animal studies have shown that VNS induces cellular and neurochemical changes in the CNS, thus providing possible mechanisms of antiseizure and neuropsychiatric effects of VNS (105). Studies in rats undergoing VNS reveal increases in cellular activity, as measured through the oncogene C-fos level, in amygdala, cingulate, locus ceruleus (LC), and hypothalamus (106). Zuo et al. (107) investigated the modulatory effect of VNS on the development of long-term potentiation (LTP) in the dentate gyrus and found that VNS modulates synaptic plasticity in the hippocampus. VNS induced an increase in the number of available progenitor cells in the adult rat dentate gyrus by a mechanism presumably involving increased progenitor proliferation. Preclinical work has also demonstrated modulation of serotonin (108), norepinephrine (79), GABA, and glutamate (109). A study of lumbar cerebrospinal fluid (CSF) analytes in epilepsy patients sampled before and after three months of VNS showed significant increases in CSF concentrations of GABA and trend-level decreases in glutamate (110). Other provocative findings from CSF studies are VNS-induced increases in levels of the major metabolite of dopamine, homovanillic acid (111), and the major metabolite of serotonin, 5-hydroxyindoleacetic acid (110), although no VNS-associated changes were observed in CSF levels of the peptide substance P (112).

Dorr and Debonnel (108) recently published their findings of increased basal firing rates of dorsal raphe nucleus and LC following long-term VNS treatment in a rodent electrophysiology study, suggesting a novel mechanism of antidepressant action. Additional recent data showed that responders to VNS exhibited enhanced P300 response to auditory evoked potentials, further suggesting that VNS has effects on electrical activity within the CNS (113). Indeed,

emerging data appear to provide converging lines of evidence that VNS exerts measurable effects in brain regions and neurotransmitter systems implicated in mood disorders. However, a putative VNS antidepressant mechanism of action remains obscure (105), as it does for ECT and TMS.

VNS surgery is considered a procedure of low complexity and is typically performed in an outpatient surgical setting with general anesthesia. A pulse generator pacemaker device is implanted subcutaneously into the left wall of the chest, posteriorly toward the axilla and is connected to bipolar electrodes, which are attached to the left vagus nerve within the neck. Two small incisions are made, one in the left neck and one in the left chest wall. A tunneling tool is used to connect the lead wires deep subcutaneously between the pulse generator site in the chest and the place of attachment on the vagus nerve. After a two-week postsurgical recovery period, the device is turned on, and stimulation is titrated to optimal treatment levels. Device "dosing"—including selection of stimulus intensity, duration, and off-interval—is noninvasive and adjusted by an external telemetric wand. A typical programming cycle consists of 30 seconds of stimulation followed by a 5-minute off period (114). Adjustments occur in the office setting so that the patient and clinician are aware of real-time adverse events prior to the patient returning home.

The safety of VNS is well established from its use in the treatment of epilepsy (115). In total, >40,000 patients have been implanted with the VNS device worldwide since the 1990s (Cyberonics, Houston, Texas, U.S.) (personal communication). The side effects of VNS are generally mild and are associated with stimulation (i.e., the "on" phase of the cycle). Voice alteration/hoarseness, dyspnea, and neck pain were the most frequently reported adverse events in a long-term follow-up study of VNS in patients with depression (116). Patients with sleep apnea may require additional monitoring when VNS is titrated (117). Adjustments in stimulation pulse width and frequency can also be performed to manage side effects and optimize therapy (114). VNS has been safely combined with ECT in some patients (118).

Data supporting the antidepressant efficacy of VNS come from open-label and naturalistic studies where the neuromodulation therapy was added to ongoing, stable doses of psychotropic medication. In an open-label pilot study, 60 patients with treatment-resistant major depressive episodes, who had not responded to at least two trials of medication from different antidepressant classes, received 12 weeks of adjunctive VNS (119). Response rates ranged from 31% to 37%, depending on the scale used. The most common side effect was voice alteration or hoarseness, which was generally mild and related to output current intensity. In a pattern similar to that described for TMS (reviewed above), VNS appeared to be most effective in patients with low-to-moderate, but not extreme, antidepressant resistance. A naturalistic follow-up study was conducted to determine whether the initial promising effects were sustained in a subgroup ($n = 30$) following exit from the three-month acute study (120). At one-year follow-up, response rates for the subgroup were sustained (40–46%) and remission rates significantly increased (17–29%), although psychotropic medications and VNS stimulus parameters varied during the follow-up interval. Subsequent follow-up data from a larger number (i.e., 59 patients from the original pilot study cohort who completed the study and who continued with adjunctive VNS) demonstrated a response rate of 44% at one year, which was largely sustained (42%) after two years of active treatment (121). Remission rates

demonstrated a similar pattern, rising to 27% at one-year follow-up and to 22% after two years of stimulation. Following these promising open-label pilot study results, a larger controlled trial was undertaken.

The large ($n = 235$) randomized, sham-controlled, multicenter study of adjunctive VNS did not find a significant difference in acute phase response between active and sham groups (15% and 10%, respectively) at the 12-week endpoint (122). However, open-label follow-up observations of this cohort over the subsequent years suggested a cumulative beneficial effect of treatment over time (116), leading to speculation that positive VNS response requires more time than that typically seen with antidepressant medications and ECT. As the initial active VNS group continued with stimulation for another nine months, the initial sham group crossed over to receive 12 months of active VNS. Participants received antidepressant treatments and VNS, both of which could be adjusted. Data from this open study revealed response rates of 27% to 34% and an open-label remission rate of 15.8% at one year (116).

In that the short acute study was negative, and the extensive long-term open-label study was promising, investigators set out to better understand the long-term effects of VNS when combined with community treatment as usual over 12 months [VNS + TAU outcomes ($n = 205$)]. These were compared with those of a similar group of patients with treatment-resistant depression, who received TAU only and without VNS (TAU; $n = 124$) in a nonrandomized, naturalistic case-control study (123). An analysis comparing the VNS + TAU group (monthly data) with the TAU-only group (quarterly data) according to scores on a self-report depression symptom scale showed adjunctive VNS associated with significantly greater improvement per month than TAU across 12 months, and response rates were 27% for VNS + TAU and 13% for TAU, supporting the finding of greater antidepressant benefit in VNS patients (123). Review of these (nonrandomized) data led to FDA approval of adjunct VNS in 2005, with an indication for treatment of depressive episodes in both bipolar and unipolar types of affective disorder.

Subsequent 24-month follow-up study of patients treated with adjunct VNS therapy found a decline in suicide attempts, diminished levels of suicidal ideation, and fewer hospitalizations for worsening depression (124). VNS recipients identified as early (i.e., by 3 months) and late (i.e., by 12 months) responders maintained their response at a rate of 76.7% and 65%, respectively, at 24-month follow-up assessment (125). Thus, while modest response and remission rates appear to accompany VNS therapy, available data suggest a high level of durability of response for those who experience clinical benefits. Widespread access to VNS for patients with treatment-resistant depression has been limited by lack of coverage by third-party payers, despite clear FDA approval and evidence suggesting potential reductions in health care costs with VNS for TRD may be substantial.

DEEP BRAIN STIMULATION

DBS is an FDA-approved treatment for tremor in Parkinson's disease, essential tremor, and dystonia, but remains investigational for psychiatric disorders. Since it requires invasive neurosurgery and associated risks, DBS is currently reserved for patients with the most severe and treatment-refractory depression in research protocols. Pilot studies of DBS for depression have included only

patients who have failed multiple antidepressant treatment courses over several modalities and classes, as well as evidence-based psychotherapy (i.e., cognitive behavioral therapy), and ECT.

Surgery to implant DBS devices occurs in two phases. First, electrodes are inserted through burr holes in the skull under general anesthesia. These electrodes are placed into targeted subcortical areas, which are guided by sterotactic positioning and MRI. After implantation and successful testing, the electrodes are connected with lead wires that are tunneled subdermally under the scalp, neck, and chest wall areas to a pacemaker-like pulse generator. As with VNS, adjustment of DBS stimulation parameters is performed via computer-controlled telemetric wand.

Because of the experimental nature of the treatment, only limited data is available for DBS as a treatment for depression. Case reports initially described improvement for patients receiving DBS for treatment-resistant MDD, tardive dyskinesia, and obsessive-compulsive disorder (OCD) (126–129). Greenberg et al. presented findings suggesting efficacy of DBS on the ventral portion of the anterior limb of the internal capsule and adjacent dorsal ventral striatum (VS) in a pilot study of five depressed patients over a three-month course (130). They targeted the ventral internal capsule, which was an area of consistent improvement of comorbid depressive symptoms in patients with treatment-refractory OCD (131). During this pilot study, all five patients demonstrated improvement in depressive symptoms, and with three of the five patients demonstrating a 50% acute response rate and the remaining two patients achieving 23% and 17% reductions in depressive scores. Not only were symptoms' scores significantly reduced, but there was a corresponding increase in ratings of social and occupational function. The five patients continued with DBS in open-label fashion, following a three-month blinded period, and additional patients were enrolled in the pilot study at a second site; preliminary data describing one-year outcomes for the expanded group ($n = 11$) of pilot patients show robust response and remission rates of 56% and 33%, respectively (132).

In a larger sample of 15 patients, Malone et al. demonstrated further efficacy of targeting DBS to the ventral capul/ventral striatum (VC/VS). Patients were followed for six months to four years, and they found significant improvements in depressive symptoms and global functioning from baseline at six months and last follow-up. They also reported that 40% of patients met criteria for response at six months, and 53% at last follow-up, with remission rates at 20% at six months and 40% at last visit, and reported that DBS was well tolerated (133).

Another group, Mayberg et al., initially examined DBS targets in the subcallosal cingulated gyrus (Cg25) in six patients with treatment-resistant major depressive episodes (134). At two months, five of the six patients met response threshold, and these effects were maintained in four of the five responders at the six-month follow-up. PET scans at three and six months demonstrated normalized blood flow in the subgenual cingulated (i.e., decrease from baseline) and prefrontal areas (i.e., increase from baseline) in a subset of responders. Data from a 12-month follow-up from these patients and 14 additional patients have recently been reported. They found that one month after surgery, 35% of patients met criteria for response, and 10% met criteria for remission, and these effects were largely maintained for the full 12-month period, and that DBS was associated with specific metabolic changes in the cortical and limbic circuits involved in depression.

DBS to the nucleus accumbens has recently been used to target anhedonia in a double-blind pilot study for treatment-resistant depression in three patients. The target is the rostral area of the nucleus accumbens, which is directly adjacent to the ventral internal capsule targeted in previous studies (131,132). In all patients, clinical ratings of depression improved when stimulation was active, beginning with the titration period and continuing through one week of active stimulation. Patients subsequently reported worsened depressive symptoms when the stimulation was turned off (129). Given the immediately observable improvement in this preliminary study, the nucleus accumbens remains another exciting target for DBS.

There are several major limitations of DBS. The risks for neurosurgery are high and include intraoperative seizure, intracranial hemorrhage, edema, infection, and death (130,135). Hardware malfunctions either during or post implantation may also be a limiting factor, and batteries require replacement every one to three years (136). As in VNS, implanting the generator may be disfiguring, depending on the location of the generator and body habitus. Transient side effects of DBS may include dose-dependent light-headedness, insomnia, and psychomotor changes. Transient hypomania resulting from changes in stimulation parameters has been reported. DBS does not appear to have any cognitive side effects, and there are reports of slight improvement of cognition during DBS treatment (137). While there is also very limited data on DBS outcomes beyond one year, the report describing three-year outcomes for the 10 patients receiving DBS for OCD suggest no cumulative side effects of treatment. Overall these results demonstrate a fairly benign profile associated with longer-term DBS of the ventral internal capsule (VC/VS) (133,135), but given the small numbers of patients enrolled in these early studies, definitive statements about longer-term efficacy and safety cannot be made at this time.

CONCLUSION

ECT remains the gold standard neurostimulation therapy for pharmacoresistant depression, but side effects of cognitive dysfunction greatly reduce enthusiasm for this treatment. Novel neurostimulation therapies, such as VNS, TMS, and DBS, hold considerable promise for the treatment of depression. Clearly, refinements in device technology and further elucidation of targets and stimulation parameters are needed, but given the promising available data, neurostimulation remains a novel and tantalizing area of psychiatry that has the potential to fundamentally change how the field treats psychiatric illness in the foreseeable future.

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10 Natural Remedies for Treatment of Depression

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INTRODUCTION

More than 70% of the world's population uses some form of complementary and alternative medicine (CAM), including natural products as well as other therapeutic interventions (1), with more modest but growing usage rates of 25% to 35% in the United States (2,3). Despite improved funding for clinical and basic research on these therapies, and the growing inclusion of CAM in medical education curricula, most physicians feel unprepared to advise patients who are using or wish to learn about alternative treatments, and many practitioners remain skeptical of their effectiveness.

The reluctance to adopt natural remedies as part of the medical armamentarium is understandable. Natural medications are generally not regulated by the U.S. Food and Drug Administration (FDA) (4,5), and given the limited body of research evidence, there is a lack of consensus on optimal doses and preparations, active ingredients, contraindications, and other safety considerations. One particularly worrisome public misconception is that alternative remedies are safe simply because they are natural. While the relatively few reports of serious adverse effects from these medications are a large part of their appeal (6,7), there are increasing cases of toxic reactions from these agents, as well as interactions with conventional medications (6,7).

Most of the available natural psychotropics target mood and anxiety symptoms. This chapter will review the efficacy and safety of the most popular and better-characterized natural medications used for mood disorders, including St. John's wort (*Hypericum perforatum*), *S*-adenosyl-L-methionine (SAMe) and the B vitamins, and omega-3 fatty acids eicosapentaenoate (EPA) and docosahexaenoate (DHA).

ST. JOHN'S WORT (*HYPERICUM PERFORATUM*)

Hypericum extract is obtained from the flower of St. John's wort (*H. perforatum* L.) (6). Physicians in Europe generally consider *hypericum* effective for mild to moderate depression, and its popularity in the United States and worldwide has increased dramatically in the past decade.

Mechanisms of Action

Hypericum extract contains polycyclic phenols, hypericin and pseudohypericin, flavinoids (hyperoside, quercitin, isoquercitrin, rutin), kaempferol, luteolin, biapigenin, and hyperforin (8–10). *Hypericin*, thought to be one of the active components, works by decreasing serotonin receptor density (11), but since it does not cross the blood-brain barrier, it may act by inhibiting production of

interleukin-6 and interleukin-1β, dampening production of cortisol via a decrease in corticotropin-releasing hormone (12). Hypericin has been proposed to have affinity for γ-aminobutyric acid (GABA) receptors, and may also inhibit reuptake of serotonin, norepinephrine (NE), and dopamine (DA) (11), resulting in downregulation of β-adrenoreceptors and increased density of serotonergic $5HT_2$ and $5HT_{1A}$ receptors (13).

Hyperforin is another potentially active ingredient of *hypericum* (14), and preparations containing 5% hyperforin have been shown to result in greater clinical improvement compared with those with 0.5% hyperforin or placebo (15). Mechanisms of antidepressant action for hyperforin may include serotonin, NE, and acetylcholine reuptake inhibition as well as inhibition of DA, GABA, and L-glutamate (16). Other proposed mechanisms include downregulation of cortical β-adrenoreceptors, $5HT_2$ receptors, and synaptosomal release (14).

Most commercially available St. John's wort preparations are standardized to either hypericin or hyperforin, but given the variety of preparations, the amount of active ingredients may vary greatly, and there are no published head-to-head trials comparing different brands. Flavinoid components of *hypericum* are MAOA inhibitors, but their concentration in the extract is so small that they are not thought to be involved in the antidepressant mechanism (17), and no special diet is required when taking *hypericum*.

Efficacy

Hypericum has generally been shown to have greater efficacy than placebo and equal efficacy to several FDA-approved antidepressants. There are approximately 35 to 40 published trials, 26 of which used placebo controls and 14 compared *hypericum* against standard antidepressants (18). Most studies have been conducted in Europe in general clinical care settings, rather than clinical research programs (6). The findings may therefore be more predictive of effectiveness and acceptability in the "real world," but may diverge widely from those of controlled research settings. The European studies also provide less detail about recruitment and randomization methods, exclusion criteria, and other study characteristics, and patient diagnoses are often not limited to major depression (6,14).

Hypericum has been compared with the tricyclic antidepressants (TCAs) imipramine and maprotiline (19–22) at doses of about 75 mg daily, which tend to be lower than those used by U.S. psychiatrists. Response rates in these trials appear comparable to those in studies that use higher doses of TCAs (e.g., imipramine >150 mg/day), though the lack of a placebo control makes it difficult to interpret the results. In these studies, response rates ranged from 35.3% to 81.8% for *hypericum* and from 41.2% to 77.8% for TCAs.

Various meta-analyses of the early *hypericum* studies have been published. Nierenberg (23) examined four studies with various depressive conditions in which *hypericum* 300 mg t.i.d. was judged significantly more effectively than placebo in 225 subjects, with *hypericum* yielding a 66% response rate and placebo only 28.8%, which are comparable to rates observed in standard antidepressant studies. Linde and colleagues (24) examined 15 trials comparing *hypericum* with placebo and 8 trials comparing *hypericum* with TCAs in 1757 patients with mild to moderate depression. In six trials with single preparations of *hypericum* (St. John's wort only), hypericum yielded response rates of 55.1% compared

with 22.3% for placebo. In active-comparator studies, *hypericum* produced response rates of 63.9% compared with 58.5% for TCAs. In two trials of combination preparations of *hypericum* (containing St. John's wort and other herbal remedies such as kava), hypericum outperformed TCAs (67.7% response vs. 50% response). Voltz, however, suggested that *hypericum* may not be effective for acute treatment of severely depressed patients (25).

In the last eight years, approximately 10 studies from North America, Europe, and South America have emerged. Many of these studies are notable for their large patient samples, randomized, double-blind, placebo-controlled designs, and comparisons between *hypericum* and newer antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs). Two studies comparing *hypericum* with placebo yielded mixed results, one suggesting a significant advantage for *hypericum* (26) and the other suggesting no advantage except for remission in completers (27). Three head-to-head comparisons between *hypericum* and sertraline (28–30) and two between *hypericum* and fluoxetine (31,32) have suggested equivalence, and perhaps even a slight advantage for *hypericum* (31), though these studies must be interpreted with caution, given the lack of a placebo comparator arm. In three three-armed studies comparing *hypericum* against an SSRI and placebo, the findings are conflicting (33–35). The Hypericum Depression Study Group found no separation of either *hypericum* or sertraline from placebo (33). Fava and colleagues (34), in a study limited by a smaller-than-projected sample, found a trend to significance for *hypericum* over placebo and a significant advantage for *hypericum* over fluoxetine. Moreno and colleagues (35) reported the worst efficacy results for *hypericum*, a mere 12% remission rate, compared with fluoxetine (34.6%) and placebo (45%).

A recent Cochrane review of these and prior studies suggested collectively similar response rates for *hypericum*, SSRIs, and TCAs, but emphasized the "inconsistent and confusing" nature of the data (18). In comparisons between *hypericum* and placebo, results tended to favor *hypericum* in studies without a strict diagnosis of MDD, but less so in trials with rigorously diagnosed Diagnostic and Statistical Manual of Mental Disorders (DSM) depression (18). More studies are necessary to better characterize the comparative efficacy of *hypericum*.

Safety and Tolerability

With *hypericum* monotherapy, adverse events are relatively uncommon and mild and include dry mouth, dizziness, gastrointestinal symptoms such as constipation, and confusion (6,36,37). So far, no published reports have assessed the effects of a *hypericum* overdose. Phototoxicity is well associated with *hypericum* in grazing animals but appears rare in humans (38). Doses as high as 1800 mg/day have caused minor increases in sensitivity to UV light in humans, but no phototoxicity per se (39). Patients who take an overdose of *hypericum* are cautioned to avoid UV radiation for about seven days (40), but this warning may not necessarily apply to patients on regular doses. As a general precaution, patients who take *hypericum* should use sunscreen and other protection when spending large amounts of time in the sun.

Several adverse drug-drug interactions between *hypericum* and other medications have been documented. These interactions seem to occur primarily via activation of the liver enzyme CYP450 3A4, which decreases activity of drugs such as warfarin, cyclosporin, oral contraceptives, theophylline, fenprocoumon,

digoxin, indinavir, and camptosar (41–46). Extreme caution is therefore required with HIV-positive patients on protease inhibitors, in cancer patients receiving chemotherapy, and in transplant patients on immunosuppressive drugs. *Hypericum* should also not be combined with SSRIs because "serotonin syndrome" has been reported, presumably due to *hypericum*'s MAOI activity (46).

St. John's wort has been associated with at least 17 cases of psychosis, 12 of which included mania or hypomania (47). Bipolar patients should therefore use *hypericum* only with a concurrent mood stabilizer.

Recommendations

Hypericum appears more effective than placebo and equivalent to low-dose TCAs, but results against SSRIs and placebo in more recent studies have been mixed, perhaps due in part to more severely and/or chronically depressed patient samples (14). Overall, *hypericum* may be most effective for milder forms of depression. Recommended doses of *hypericum* range from 900 to 1800 mg/day, usually divided on a twice- or thrice-daily basis. Despite its benign side effect profile, patients on multiple medications need to beware interactions, and bipolar patients must be watched for cycling. Additional clinical trials comparing *hypericum* against newer antidepressants as well as longer-term continuation treatment studies are warranted.

SAMe AND THE B VITAMINS

SAMe (Fig. 1) is a methyl donor thought to participate in the synthesis of hormones, nucleic acids, proteins, phospholipids, and neurotransmitters, particularly NE, DA, and serotonin (5HT) (48). Despite long-term use as an antidepressant in Europe, SAMe has achieved popularity in the United States only in the past decade (48).

Mechanisms of Action

SAMe is synthesized from the amino acid L-methionine through the one-carbon cycle, a metabolic pathway dependent on the vitamins folate and B_{12} (48), deficiencies of which have long been associated with depression. About 10% to 30% of depressed patients may have low folate and may respond less well to antidepressants (49). Deficiency of the B_{12} derivative methylcobalamin, also involved in neurotransmitter synthesis, may result in an earlier onset of depression (50). These deficiencies may lead to reduced SAMe, hence to impaired neurotransmitter synthesis that may be corrected with replenishment. Low SAMe levels have been found in the cerebrospinal fluid of depressed people (51), and higher plasma SAMe levels have been associated with improvement of depression (52). If correction of B-vitamin deficiencies can

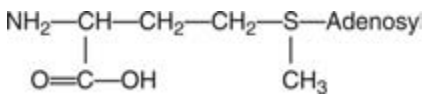

FIGURE 1 *S*-adenosyl-L-methionine. This derivative of the amino acid methionine is found in all mammals, and functions largely by donating a functional methyl ($-CH_3$) group in a variety of metabolic reactions, including neurotransmitter synthesis.

increase SAMe levels and alleviate depressive symptoms, direct administration of SAMe might also relieve depression.

Efficacy

There are approximately 45 published randomized, placebo-controlled clinical trials of SAMe for treatment of depression, most with sample sizes ranging from 40 to 100 patients, and several of which used an active comparator (48,53–55). Some early studies were limited by problems with dissolution and stability of oral SAMe (48,54,55), but the current oral preparations are tosylated and more stable. SAMe appears superior to placebo and equivalent in efficacy to TCAs (48,54,55). SAMe doses, administered orally, intramuscularly, and intravenously, range from 200 to 1600 mg/day (48,54,55).

SAMe may have a relatively faster onset of action than conventional antidepressants (48,54–56), and the combination of SAMe and low-dose TCA against TCA alone has shown an earlier onset of action for the combination therapy (57,58). Published comparisons of SAMe against newer antidepressants are lacking, but such studies are in progress. Alpert and colleagues (59) examined the efficacy of SAMe as an adjunctive treatment for 30 partial and nonresponders to SSRIs, with strong response and remission rates of 50% and 43%, respectively, and good tolerability. Placebo-controlled follow-up studies are in progress. Other reports suggest that SAMe may be effective for relieving psychological distress in patients with dementia and Parkinson's disease and in people undergoing opioid or alcohol detoxification (55).

While folic acid supplementation has benefited depressed people with folate deficiency (60), there are only three published clinical trials examining folate administration in normofolatemic depressed patients (61). A double-blind, randomized, controlled trial (RCT) (62) showed efficacy of 500 μg/day of folate augmentation in 127 partial responders to fluoxetine; an open trial administering 15 to 30 mg/day of folinic acid augmentation to 22 SSRI partial responders also suggested benefit (63); and a comparison between 50 mg/day of 5-MTHF (methyltetrahydrofolate) augmentation versus trazodone 100 mg/day in 96 subjects with mild to moderate dementia and depression found no significant difference between the two therapies (64). Further investigation in larger samples is necessary to confirm and expand on these encouraging findings.

Safety and Tolerability

SAMe is well tolerated with few adverse effects, which may include gastrointestinal upset, insomnia, loss of appetite, constipation, dry mouth, sweating, dizziness, and nervousness (48). Increased anxiety, mania, and hypomania have been reported in bipolar patients (48,65,66), and these individuals should take SAMe only with a concurrent mood stabilizer. SAMe has not demonstrated hepatotoxicity, anticholinergic effects, or significant interactions with other medications. Folic acid appears to be equally well tolerated and safe, with little evidence of adverse effects or interactions.

Recommendations

SAMe appears effective for treatment of major depression, both as monotherapy and as augmentation for standard antidepressants. Given its high tolerability

and benign side effect profile, it may be especially suited for patients who are sensitive to antidepressant-related side effects, particularly the elderly and those with medical comorbidity. Recommended doses range from 400 to 1600 mg/day (48,54,55), though in clinical practice we have observed individuals who require doses in the range of 2000 to 3000 mg/day or higher. Investigation to determine optimal SAMe doses and comparisons with newer antidepressants are in progress, as are studies of new preparations of folic acid as antidepressant augmentation agents.

OMEGA-3 FATTY ACIDS

The modern Western diet, relatively poor in omega-3-containing fish and rich in processed foods containing omega-6 fatty acids, has resulted in a higher plasma ratio of omega-6:omega-3 (n-6:n-3) in Western countries compared with countries with higher fish consumption (67–71). This, along with the additional stresses of modern life, has been suggested to put humans in a "pro-inflammatory" state that may contribute to cardiovascular disease as well as mood disorders (72). Omega-3 supplementation may potentially reverse this state and related illnesses by correcting the n-6:n-3 ratio. Over the past decade, there has emerged encouraging evidence of clinical efficacy for eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Fig. 2), two omega-3s found primarily in fish oil.

Mechanisms of Action

Omega-3 fatty acids may exert their antidepressant effects by various mechanisms. They have been shown to influence membrane-bound receptors and enzymes involved in the regulation of neurotransmitter signaling, as well as regulation of calcium ion influx through calcium channels (72). Administration of EPA and DHA to healthy subjects has resulted in a lowering of plasma NE levels, suggesting that omega-3s may also exert some effects via the catecholamine system (73). Omega-3 fatty acids may also inhibit secretion of inflammatory cytokines, dampening adrenal corticosteroid hormone release and its related mood-altering effects (72,74).

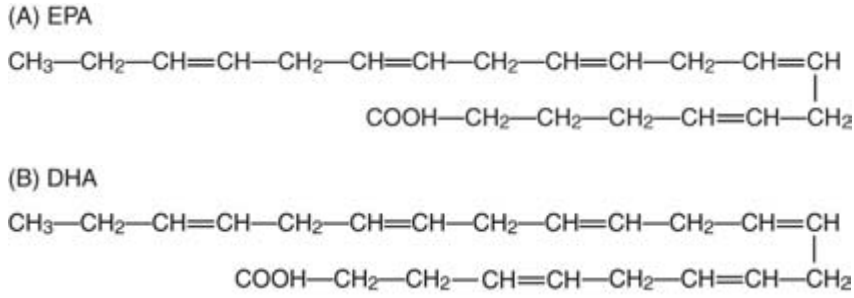

FIGURE 2 Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). (**A**) EPA (20:5, n-3) consists of a 20-carbon chain and five double bonds. In the above orientation, carbons are numbered by convention from left to right, with the leftmost one called the "omega" carbon. "Omega-3" refers to the first double bond, which occurs on the third carbon from the left. (**B**) DHA (22:6, n-3) consists of a 22-carbon chain and six double bonds. The first double bond occurs on the third carbon from the left.

Efficacy

Approximately 15 to 20 randomized, placebo-controlled trials and a few open studies with EPA and/or DHA suggest that omega-3 supplementation at doses about five or more times the current U.S. dietary intake may yield antidepressant and/or mood-stabilizing effects, particularly as adjunctive therapy (75).

A number of meta-analyses of omega-3 RCTs for depression (75–78) suggest efficacy over placebo, but are limited by several factors, such as the combination of augmentation and monotherapy trials and the inclusion of bipolar samples in some cases. Most of the trials reviewed are small, with a wide range of omega-3 preparations and doses (1–10 g/day). Publication bias was also noted as a major limitation. The findings overall are encouraging, but the heterogeneity of the studies dampens the cogency of the body of data.

Notable studies include Peet and Horrobin's (79) 12-week randomized, placebo-controlled, dose-finding trial of ethyl-EPA adjunctive therapy for 70 adults with treatment-resistant depression. Optimal efficacy (53% response rate) was observed for doses of 1 g/day, with weaker response rates at doses of 2 and 4 g/day or placebo. These results suggest a therapeutic window for omega-3 and that "overcorrection" of the n-6:n-3 ratio may limit the antidepressant effect of EPA. Other studies, however, have also suggested efficacy of EPA in doses of 1 to 2 g/day (80,81) or higher (82).

Regarding DHA, which is relatively understudied compared with EPA, one RCT with 36 subjects showed lack of efficacy of 2-g/day DHA monotherapy for depression (83). A more recent three-armed pilot dose-finding study of DHA monotherapy (84) found a response pattern similar to Peet and Horrobin's results for EPA (75), with the greatest efficacy for DHA doses of 1 g/day compared with 2 and 4 g/day (84), which also suggests possible overcorrection in the patients from Marangell et al. (83).

Studies of omega-3s in postpartum depression have yielded mixed results. Freeman and colleagues (85) compared doses of 0.5-, 1.4-, or 2.8-g/day omega-3 in 16 women, with good response in all groups. Conversely, an open study (86) of 2960-mg/day omega-3 mix (EPA and DHA) in a small sample of pregnant women suggested no preventive effects for postpartum depression.

Findings in bipolar disorder have also yielded mixed results. A high-dose omega-3 adjunctive mix (6.2 g EPA + 3.4 g DHA) in 30 patients over four months resulted in a significantly longer duration of remission for those receiving omega-3 compared with placebo (87). More recent RCTs, however, have not provided a conclusive replication of these findings on a larger scale (88,89). Recent reviews of bipolar studies (90,91), including a Cochrane review (91), have suggested that omega-3's main benefit in bipolar patients is with regard to depressive rather than manic symptoms.

Omega-3 fatty acid treatment has been examined in a range of other psychiatric syndromes, such as borderline personality disorder, schizophrenia, attention deficit disorder (ADD), and obsessive-compulsive disorder (OCD), with equivocal results (92–99). These investigations, like most omega-3 studies, were limited by small patient samples.

Safety and Tolerability

The omega-3s have an excellent safety and tolerability record thus far. Complaints such as gastrointestinal upset and fishy aftertaste tend to occur with

higher doses (>5 g/day) and with less pure preparations. At doses of 1 g/day with highly purified omega-3 preparations, these side effects are less common (75). There is a minimal risk of bleeding, particularly with doses higher than 3 g/day. Individuals taking anticoagulants should therefore not use omega-3s without physician supervision (75). A few cases of cycling in bipolar patients (75) have suggested that omega-3s be used with care in this population, preferably with a concurrent mood stabilizer.

Recommendations

Omega-3 fatty acids, particularly EPA, appear effective and well tolerated as antidepressant monotherapy or adjunctive therapy. Freeman and colleagues (75) recommend that depressed individuals may use approximately 1 g/day of an EPA-DHA mixture, but should not substitute omega-3s for conventional antidepressants until more rigorous studies emerge. Likewise, doses greater than 3 g/day should be taken under a physician's supervision (75).

Depressed populations that may be especially well suited to the omega-3s may include pregnant or lactating women for whom antidepressants must be used with caution (100), elderly individuals prone to side effects from standard antidepressants, and people with medical comorbidities such as cardiovascular disease and autoimmune conditions, for whom there may be dual benefits, though studies in these populations are lacking.

At this time, further study of the efficacy of omega-3 *monotherapy* is sorely needed, as well as comparisons between EPA and DHA, and examinations of the mechanism of action of the omega-3s, particularly regarding the immune system. A clinical trial addressing these questions is in progress at the Massachusetts General Hospital and Cedars-Sinai Medical Center. It is hoped that these and other investigations will begin to answer some of the lingering questions about this potentially valuable treatment.

SUMMARY AND CONCLUSIONS

Natural medications may eventually prove a valuable addition to our pharmacological armamentarium. Current research data by and large suggest efficacy and safety, but we need more well-designed, controlled studies on large patient samples to provide more conclusive recommendations.

For now, the best candidates for alternative treatments may be those with mild illness and a strong interest in natural remedies. For these patients, a failed trial of a natural product would not be devastating. Refractory patients who have not responded to many conventional antidepressants and/or are prone to bothersome side effects may also benefit, but it must be emphasized that alternative agents seem best suited for the mildly ill (101). Patients who are taking multiple medications should have close monitoring, in view of the growing evidence of drug-drug interactions, and as much as possible, natural medications should be used under physician supervision.

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11 Depression and Anxiety

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INTRODUCTION

This chapter, in my opinion, is born out of necessity. A few years ago, we designed and opened a treatment-resistant depression program at our institution. It became readily apparent that finding patients with "just" depression and without comorbidities was almost impossible. We screened and diagnosed most patients who ultimately had findings consistent with comorbid anxiety and depression and found that we were more uniformly treating this comorbidity. We ultimately opened an anxiety program as well. A literature search at the time suggested that Tucker et al. (1) had found similar results when they studied and compared their two specialty clinics, one for anxiety and one for depression.

It became more frustrating in that there is a surprisingly small literature evidence base regarding comorbid anxiety and depression and certainly no Food and Drug Administration (FDA) approval or even manualized psychotherapies that address both illnesses as a single population. On another note, this chapter will be short. Upon reviewing other written reviews regarding treatment options for truly comorbid anxiety and depression, we have found that most other reviews quote many randomized controlled trials (RCTs) as being effective for depression *or* anxiety, not depression *and* anxiety. For example, a review may comment that paroxetine has adequate RCTs for the treatment of major depression, panic, posttraumatic stress, and social anxiety. Despite these trials being conducted on noncomorbid patients, many authors assume that the drug, and others like it, will work in the comorbid state. This review, in general, will not reference articles unless the patient population studied was truly comorbid. Sometimes studies refer to "depression with comorbid anxiety" to mean anxious features driven by the original depressive symptoms. In this review, we will focus on "comorbidity" meaning both anxiety and depressive disorders occur simultaneously but are expressed as independent entities.

We suspect that the comorbid state will be harder to treat and have poorer outcomes, which is common in medically comorbid states, and suspect that the economic cost of mixed anxiety and depression (MAD) is quite high (2). MAD is discussed further later but is a subsyndromal form of depression combined with anxiety and is felt to be the cause of one-fifth of absentee dates in the United Kingdom. These MAD patients had poorer health, more suicide attempts, and more unemployment than patients with a single axis I disorder. Canadian data (3) suggests that depressed patients had the greatest comorbidity with social and generalized anxiety, and truly comorbid patients scored significantly higher on distress scores, daily activity limitations, and disability days, similar to the U.K. group. Medical comorbidity and utilization also increase with depression and anxiety comorbidity per Katon et al. in regards to diabetes, pulmomary disease, heart disease, and arthritis (4). A Norwegian

study (5) found a seasonal association of increased comorbid depression and anxiety in spring and fall seasons with a clearly associated suicide rate as well. In fact, suicidality in panic was recently addressed in another Canadian study (5), which determined uncharacteristically that panic had very low rates of suicidality but found that when depression becomes truly comorbid, the rates increase dramatically. Over half the patients in this study reported a history of suicidal thoughts, and 34% had attempts. Less dangerous but possibly more impairing on a day-to-day basis is the finding that patients with comorbid social anxiety and depression do much more poorly on neuropsychological testing than either disorder alone (6). The elderly show a similar pattern with major depressive disorder (MDD), causing linear degradation in cognitive abilities. Anxiety caused a curvilinear effect where mild anxiety increased cognition but anxiety greater than this caused degredation. The authors found that the presence of MDD worsened cognition in anxiety patients overall (7). In a cognitive model, negative schema are known to promote pathological anxiety. In social anxiety, patients assume the worse about social interactions. Wilson and Rapee (8) determined that comorbid depression caused a significant increase over anxiety symptoms alone in socially anxious patients' beliefs that social events would be negative, they would be evaluated negatively by others, and adverse events would occur in the future as such. Similarly, adding depression to obsessive-compulsive disorder (OCD) may be detrimental as well. Massellis et al. (9) determined that depression caused greater disruption to quality of life than did the premorbid obsessions or compulsions in their study. Finally, there may also be gender differences in this area. Women usually outnumber men for reported individual psychiatric anxiety and depressive disorders. It is also clear that the women present with more comorbidity. In the Netherlands, 5.1% women versus 1.9% men were found to have true depressive and anxiety comorbidity (10). Given the clearly additive negative effects of true comorbid depression and anxiety, the goal of this chapter is to review what there is of the literature regarding phenomenology, epidemiology, and treatment options. Secondarily, we will discuss possible treatment approaches where literature is unavailable. The currently accepted DSM-IV-TR (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*) (11) manual suggests that there are three types of depression (MDD, dysthymic disorder, and depressive disorder NOS) and six types of anxiety [generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), OCD, posttraumatic stress disorder (PTSD), and anxiety disorder NOS]. This chapter will, at times, overly simplify that depression plus anxiety is a generic state. As most clinicians know, many treatments that help one anxiety disorder may ultimately help other anxiety conditions as well. We also know that there are nuances when treating these separate anxiety disorders and admit up front that there is very little data focusing on depression and specific anxiety disorder comorbidity.

EPIDEMIOLOGY

Sanderson et al. (12) noted that in 260 depressive patients, approximately 62% also had concurrent axis I disorders, a majority of which were anxiety related. GAD is often found in 50% or more of MDD patients (13), and in fact, this

combination of MDD and GAD may be the most commonly occurring psychiatric disorder. Fawcett and Kravitz (14) also found that worry, psychic anxiety, and somatic anxiety were present in a majority (42–72%) of MDD patients. Joffe found the same in 31% of MDD patients (15). Kessler et al. (16), furthermore, found that MDD often follows onset of an anxiety disorder, or is, in fact, secondary to the index anxiety episode. We often view depression as the more severe, paramount, or premorbid condition when, in fact, anxiety may be an independent driving force behind an index episode of depression and may also confound and worsen the episode, as noted in the introductory paragraphs. It also makes sense, as in the world of medical comorbidities, that in psychiatric comorbidities, outcomes are often worse. Investigators (17,18) suggest that when comorbidity of MDD and anxiety disorders exist, a more chronic disease course may ensue, worse outcomes and recovery may result, and suicide rates may increase. Regarding suicide in this population, Fawcett (19) offers a nice paper, which reviews the epidemiology, risk, and biological etiology of how anxiety and agitation promote worsening of depressive states and may be a key risk in promoting suicidality.

RECOGNIZING COMORBID ANXIETY AND DEPRESSION

It would be easier than using the DSM-IV-TR if we were to conceptualize everyone with a mixture of depression and anxiety as the ICD-10 (*International Statistical Classification of Diseases, 10th Revision)* allows for the diagnosis of MAD (20,21), though this syndrome is characterized by mild or subsyndromal mixtures of anxiety and depression and may not capture full syndromal features of patients who have both illnesses concurrently. The authors will stick with research-based DSM-type criteria, and where criteria are met, full diagnostic labels be applied.

Some often-used clinical conventions may help conceptualization of these comorbid states. These conventions may modify the idea that if all DSM symptoms are met, then all diagnoses "count." For example, it is important to take a lifetime history of mood and anxiety disorder episodes instead of just current symptoms. As noted above, many patients have premorbid anxiety symptoms, if not frank disorder. It is much more likely that if patients have premorbid PD, for example, when they are diagnosed later as having depression and panic simultaneously, they have, in fact, two separate psychiatric illnesses, that is, PD and MDD. The opposite is likely true in that depression may also be the great pretender for producing secondary anxiety. In fact, most research depression-rating instruments, like the Hamilton and Montgomery scales, measure several anxiety symptoms as well as the classic depression ones. It is quite possible that in a patient with no premorbid anxiety in his or her first major depressive episode (MDE), anxiety symptoms will actually be driven by the underlying depression. Specifically, if a patient develops depression first and then begins having panic attacks, obsessive or ruminative worrying, or social anxiety, it is likely that he or she has one diagnosis—MDD. The MDD is thus causing the anxiety symptoms, and only one diagnosis is given. In the literature, this condition is often called depression with anxious features, or misnamed depression with comorbid anxiety—implying that a separate anxiety disorder is occurring. The convention of clinical choice is that if the MDD comes first and anxiety second, then all is subsumed under the MDD solo diagnosis.

However, there is no data to corroborate or determine the accuracy of this convention.

Biologically speaking, which illness comes first may not make a large difference as often the same type of medications or psychotherapy may be used to treat both. The work of Stephen Stahl (22) might provide a rationale. If we are to think of symptoms instead of syndromes, we can deconstruct the latter into the former and map this to known transmitter, receptor, or neuroanatomic abnormalities or even endophenotypes with the advent of neuroimaging, pharmacogenetics, etc. If we look at serotonin deficiency, we might expect to see abnormalities in low transmitter levels, high receptor levels, or frankly malfunctioning neurocircuitry between cortical and limbic structures. When any of these go awry, worry, agitation, panic, and insomnia may ensue. Descriptively, if we look at the DSM diagnosis of MDD, we will see symptoms of insomnia and psychomotor agitation. So, if dysfunctional serotonin neurocircuits can cause agitation and insomnia in MDD, why is the same possible for GAD or PTSD as well? There may be a common vulnerability in this circuitry that may cause depression in one patient, anxiety in another, and comorbidity in a third. It makes sense that these illnesses overlap and are often comorbid given some of these biological theories. Another example would be that of poor concentration and inability to focus or even make decisions. This symptom is found overlapping in MDD, GAD, PTSD, etc., as well. We might find dysfunctional noradrenergic symptoms underlying this symptom, which may then contribute to any of these syndromes similar to the serotonin story noted above.

In regards to detection, a thorough DSM descriptive interview is warranted while keeping this theoretical biology in mind. Also, knowing the clear epidemiological comorbidity rates, one should assume that where one finds depression, one will likely find anxiety. Using the DSM and the conventions noted above, an accurate set of diagnoses may be applied. If a clinician wants to increase accuracy, then rating scales may be used to help delineate depression versus anxiety or measure each syndrome separately. Rating scales will be thoroughly discussed in one of the next chapters, but we will offer some of our clinical ideas below as an introduction.

The Covi-Raskin scales (23) approach is to use simultaneously two scales that measure anxiety and depression and to see where more symptoms exist. This is a clinician-administered scale, which is often used in research trials to determine which diagnosis is of primary importance. An easy patient-administered scale is the hospital anxiety and depression scale (HADS) (24), which measures both anxiety and depression in a 10-question scale. It was designed for primary care and is simple to score. The author is reasonable in assuming that the average psychiatrist does not like to complete rating scales and that, with time pressures, conducting clinician-administered scales in an office visit is difficult and unwieldy. Despite these clinician scales being the research gold standard, we suggest much more use of patient-completed scales, like the HADS. Patients can be asked to come earlier to complete these scales in the waiting room. A support staff employee or the clinician may score these within seconds, and no time from the session is lost. Depending on the scale used, many of the depression and anxiety symptoms are asked on these scales already, so re-asking verbally in session is not needed unless further clarity is needed on an item, i.e., if suicidality is acknowledged on the scale. It is likely that a patient-rated public domain, or free scale, exists for every DSM anxiety disorder.

For example, the Penn State Worry Questionnaire (25) for GAD, the Padua Inventory for OCD (26), and the Mobility Inventory for PD (27) are easy to use. For MDD we have grown fond of the Inventory of Depressive Symptoms by Rush, which has now been shortened to the QIDS (28). These are simple to apply in the waiting room and score quickly at entry into the office. This information is clinically very useful. In the chapter on rating scales, you will notice that routine use of scales is likely to be associated with better diagnosis and treatment outcomes. In most other medical specialties, clinicians rely on physical examination, vital signs, and blood tests, and where abnormalities are detected, more aggressive treatments are applied and, likely, better outcomes occur. The more one tests, the more abnormalities are found where we realize the patient is not in remission. In psychiatry we do not have much in the way of laboratories or blood pressure cuffs for detecting mental illness, and rating scales would serve us well as our next closest alternative. A final note regarding diagnostic rating scales, as compared with outcome rating scales, is warranted. The authors would never expect a clinician to administer a research standard MINI (29) or SCID (30) in a session because of time constraints, but patients could complete at home, or in a waiting room a full axis I and II screening instrument to aid in patient interviewing instead. We preferentially use the Personality Diagnostic Questionnaire-4 (PDQ-4) (31) and the Psychiatric Diagnostic Symptom Questionnaire (PDSQ) (32) as patient-rated axis II and axis I prescreens, respectively. These are copyrighted and are more cumbersome to score but continue to help us at time of admission to better assess comorbidity. They are often mailed out with an "admissions packet" where we ask for demographics, insurance information, background information, and these baseline screenings for axis I and II disorders. At the first visit, we have a wealth of information and a general sense of where comorbidity lies.

TREATMENT

Treating comorbid depression and anxiety patients can be easy, or difficult. Many of the FDA-approved selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) medications carry labeling showing that they may treat MDD, PTSD, GAD, OCD, SAD, and PD as individual illnesses. There is no FDA approvals for comorbid illnesses. CBT psychotherapy may be used for these individual illnesses and are manualized for them as individual illnesses. Like medications being similar in nature, that is, SSRIs and CBT techniques are similar and used for both depressed and anxious conditions but again are not often studied in the true comorbid state. Another manualized therapy, interpersonal psychotherapy (IPT), has been studied in adolescents in a controlled trial where subjects were truly comorbid with anxiety and depression and the IPT technique was not found to be significantly effective in the comorbid state. This may be an example where we might assume that therapy can help both conditions simultaneously, but in this case, one therapy may not "fit" or treat two simultaneous disorders (33). There are likely differences between PD and MDD versus SAD and MDD, but data is very much lacking. Below, we will cover what very limited results could be gleaned from a MEDLINE search regarding these comorbidities.

Montgomery and Judge (34) conducted a meta-analysis and suggested that SSRIs and tricyclic antidepressants (TCAs) are equal in outcomes in regards to treating anxiety secondary to MDD. We will stop at this point to note that there

are several RCTs in the area of anxious features of depression being treated where SSRIs, SNRIs, bupropion, TCAs, and even benzodiazepines exist and have shown that these agents work well in both symptom categories (35–37). Again, these do not address true comorbidity, but rather Hamilton or Montgomery rating scale delineated anxious symptoms that may be associated with MDD. The few articles below are worth being noted in that they do address true comorbidity.

OBSESSIVE-COMPULSIVE DISORDER AND DEPRESSION

Twenty-two to seventy-five percent of patients with OCD will have simultaneous overlap with MDD or a sequential history of MDD (38). It is well established that high doses of serotonergic agents like SSRIs and some TCAs are affective and FDA approved for treating OCD. All are also FDA approved to treat MDD. Fluvoxamine is not FDA approved to treat MDD but is approved for OCD. There are no distinct trials where MDD subjects were allowed to enroll in OCD fluvoxamine studies. It should be noted that mild depressive symptoms were noted in these studies but were not used as outcomes. In general, it was felt that as OCD symptoms improved, so did subsyndromal MDD symptoms (39). Fluoxetine has been studied in comorbid OCD and MDD, and at least three controlled studies exist. In the largest, patients with MDD that developed after premorbid OCD were included, and fluoxetine was superior to placebo for treating both MDD and OCD. The primary focus of this study, as well as the others, was in regard to OCD as the primary outcome. The authors conducted a further analysis and determined that fluoxetine's anti-obsessional qualities were distinct from its antidepressant qualities (40). The other SSRIs have very limited and often uncontrolled data.

In regard to OCD, except for the above noted studies, there are no well-controlled studies in the OCD-MDD area where primary depression was allowed. Many editorial papers exist and suggest the premise that if an agent is independently studied for each separate disorder, then it must work in the comorbid state as well. Under this rubric, we could expect, on the basis of FDA approvals, fluoxetine, sertraline, and paroxetine to work well.

GENERALIZED ANXIETY DISORDER

Over 90% of patients with GAD have other anxiety disorders, and greater than 50% will have depression (13). A quick comment about benzodiazepine sedative-hypnotic use is warranted here. Sedatives are rarely used in OCD treatment, but for the next anxiety disorders discussed, they may more often be used initially in treatment to reduce symptoms quickly or to cover SSRI- or SNRI-induced agitation, which may develop as an adverse effect early in treatment (41). It is clear that sedatives help these anxiety disorders as monotherapy and adjunctive therapy, but sedatives are unlikely to treat MDD as a monotherapy. As noted above, acute anxiolysis may also be useful in decreasing agitation regardless of primary disorder. This may allow a rapid decrease in some symptoms, calm the patient, and mitigate suicidal thinking.

In regard to GAD, there are no well-controlled studies in the GAD-MDD area. A small open-label pilot using escitalopram in the elderly with GAD and MDD showed improvement in anxiety, depression, and social-functioning ratings (42). Many editorial papers exist and suggest the premise that if an agent is

independently studied for each separate disorder, then it must work in the comorbid state as well. Under this rubric, we could expect, on the basis of dual FDA approvals, venlafaxine, paroxetine, duloxetine, and escitalopram to work well, but not buspirone, bupropion, and benzodiazepines, as they do not have many RCTs in both independent areas.

PANIC DISORDER

CBT has been studied in a small group of patients with clear comorbid MDD and PD (43). Treatment and outcomes were naturalistic and over one year's time. Patients with and without comorbidity improved equally on self-report measures, though comorbid patients had a greater severity level at CBT initiation.

Transcranial magnetic stimulation (TMS) has been studied in a single patient case study with comorbid PD and MDD following myocardial infarction (44). This patient was treated prior to TMS with sedatives, TCA, SSRI, and SNRI to no avail, and then twice-daily rTMS was started over left prefrontal cortex for three weeks. The patient was considered a responder to treatment after these three weeks, and it was continued an extra six weeks for maintenance. Many editorial papers exist and suggest the premise that if an agent is independently studied for each separate disorder, then it must work in the comorbid state as well. Under this rubric, we could expect, on the basis of dual FDA approvals, venlafaxine, paroxetine, and sertraline to work well, but not fluoxetine, escitalopram buspirone, bupropion, duloxetine, or benzodiazepines as they do not have many RCTs in both independent areas.

SOCIAL ANXIETY DISORDER

Schneier et al. (44) conducted a small open-label citalopram trial in comorbid SAD and MDD patients and found a 67% response rate for SAD symptoms and 76% for MDD symptoms in a truly comorbid population. Many editorial papers exist and suggest the premise that if an agent is independently studied for each separate disorder, then it must work in the comorbid state as well. Under this rubric, we could expect, on the basis of dual FDA approvals, venlafaxine, paroxetine, and sertraline to work well, but not fluoxetine, escitalopram buspirone, bupropion, duloxetine, or benzodiazepines as they do not have many RCTs in both independent areas.

CONCLUSIONS

As the last line in each of the above sections suggests, many previous reviews will suggest that (*i*) many of our psychotherapies and medications will allow similar outcomes and adequate treatment of anxious features because of depression or (*ii*) that if RCT and FDA approvals exist for each condition separately, then using a medication or psychotherapy proven in both areas will work in the truly comorbid patient. While we would suggest that this is likely true given the caveat, especially for item (*ii*), that outcomes such as response, remission, time to response, overall symptom burden at final outcome, maintenance of response remission, time to relapse, etc., will likely be statistically and clinically worse for those with true comorbidity. Given the sparsely available RCT in this area and given these likely poorer outcomes, it makes more clinical sense to be more astute

and aggressive in detecting residual symptoms, either by clinical prowess or by routine use of rating scales. Rational use of polypharmacy is likely the norm, and employing psychotherapy either simultaneously or sequentially makes sense as well. Once remission occurs, again rigorous attention to pending relapse should be the rule and therapy or medication changes should be employed early in initial stages to prevent full syndromal relapse. Finally, given that the FDA does not allow RCTs for seeking approvals in comorbid conditions, we are unlikely to see corporate-funded definitive trials in a comorbid depressed and anxious patient population. The National Institute of Health (NIH) has not sponsored large-scale trials in this area either, which is disappointing and also unlikely to change in the near future. Until then, we suggest using the available limited-strength comorbid trial data noted above and the single illness RCT data as the best available options. Secondarily, a rational pharmacodynamic target symptom approach in treating these patients in day-to-day practice is warranted.

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12 Depression and Chronic Medical Illness

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INTRODUCTION

It has been emphasized time and again the profound impact that depressive and anxiety disorders may have on patients with chronic medical illness. As depression is often a treatable illness, understanding the prognostic significance of depression in relation to morbidity and mortality is important certainly to each individual patient and from a public health standpoint, as depressive comorbidity often increases societal cost because of health care and disability entitlements, absenteeism, and lost work productivity. It makes intuitive sense, and as you will see throughout this chapter, there is clear evidence that depressive disorders and chronic medical illness can cause increased mortality, morbidity, medical costs, somatic symptoms, problems with adherence to treatment regimens, functional impairment and an overall decrease in quality of life. Major depression has also been shown to adversely affect the habituation process to persistent aversive symptoms such as pain or fatigue, in patients with chronic medical illness that hinders their recovery (1). Multiple studies have reported that patients with depression and anxiety disorders have significantly more unexplained physical symptoms than those without these mental disorders (2). Furthermore, increasing numbers of depression symptoms are associated with increasing numbers of unexplained physical symptoms. In another study, persons younger than 30 years were more depressed, worried, and developed more long-term mental health symptoms than other medically ill age groups (3). Also, patients with depression are less likely to adhere to medication regimens, which is a long-held idea as to the ultimate cause of increased morbidity and mortality in this population.

Studies have supported that effective treatment of depression in patients with chronic medical illness decreases the burden of chronic aversive symptoms of the medical illness. It has been shown that primary care patients with a diagnosis of depression had higher annual medical costs than patients without a depression diagnosis (4). The importance in understanding this relation also lies in the fact that primary care physicians and specialists are likely to misdiagnose major depression when patients are suffering from a chronic medical illness compared with acute medical illnesses. A lack of an accurate diagnosis may lead to overtesting and unnecessary medication changes as well, where addressing the depression simultaneously would have been warranted. Even when the effect of physical illness is controlled, it is likely that the depressed will have a significantly higher mortality rate (5).

There is common knowledge that periods of stress are related to exacerbations of asthma, arthritis, allergies, migraine, etc. Unfortunately, there is no comparable biological model to account for relationships between psychological factors and excessive immune response in a human model. There have been a few animal studies that have demonstrated clear relationships between various

stresses and immune dysfunction. If depression and anxiety allow for chronic stress and if this persists for longer periods, then one might expect it to influence a patient's susceptibility to selected morbidities due to immune issues (6,7).

Given these initial impact statements regarding the overlap between depression and medical illnesses, this chapter will next attempt to cover some selected medical illnesses and how depression negatively affects their outcomes. We will discuss a few key, chronic medical conditions and some of the relevant literature regarding depression's impact on the premorbid medical condition. This chapter is not meant to be exhaustive, but to describe in brief this medical-psychiatric interaction. Finally, the authors will make some treatment comments where applicable in hopes of allowing better understanding of this comorbid process and how to treat patients more effectively.

DEPRESSION AND CORONARY ARTERY DISEASE

Major depressive disorder (MDD) is present in as many as 20% of patients with cardiovascular disease (CVD). There may be a significantly larger number with subsyndromal symptoms (8–10). Mortality rate among post–myocardial infarction (MI) patients with MDD is fourfold compared with post-MI patients without MDD, when controlling for severity of coronary disease (13). Patients with comorbid MDD have been found to be less compliant with drug regimens and more likely to drop out of cardiac rehabilitation programs. A majority of the studies report a significant increase in deaths due to depression coexisting with CVD (11). Evidence from review of literature suggests that depression, as a coronary disease risk factor, is solid from the point of view of strength of association, prediction, consistency, and dose-response effect, and the evidence on specificity and biological plausibility is fair (12). It has been shown that MDD is a chronic, disabling condition that is associated with poor quality of life, functional limitations, less favorable self-care behaviors, and higher health care costs among patients with CVD (13,14). Depression has also been associated with the development of congestive heart failure (CHF) and with adverse outcomes in patients with CHF.

Several biological mechanisms have been identified as candidate mechanisms by which depression may lead to cardiac events, such as alterations in cardiac autonomic tone, overlapping genetic vulnerability, enhanced activity of the hypothalamic-pituitary axis, greater platelet activation, increased catecholamine levels, increased whole blood serotonin, inflammatory processes, lower omega-3 fatty acid levels, mental stress–induced ischemia (15). Potential behavioral mechanisms that may contribute are diet, lack of exercise, medication nonadherence, poor social support, and unhealthy lifestyle (15).

A recent American Heart Association science advisory recommended that screening for depression be routinely considered in patients with CVD (16). Whether this is of ultimate benefit to these patients is likely but from a research point of view is still unknown (17).

Many studies have been conducted to test the efficacy of various antidepressant treatments (ADTs) in CVD. Selective serotonin reuptake inhibitors (SSRIs) are safe and effective medications for depression in patients with heart disease (18). No evidence suggests that one SSRI is more effective than another (19). However, escitalopram and sertraline are the least likely to inhibit cytochrome p450 enzymes, thus minimizing exposure to pharmacokinetic

interactions in cardiac patients taking multiple drugs (20). Strik et al. compared the efficacy and safety of fluoxetine administered to patients after their first MI (21). The Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) tested the efficacy and safety of sertraline in patients with unstable ischemic heart disease and MDD (22). It would be worthwhile to mention that a recent randomized control study involving use of citalopram and interpersonal psychotherapy (IPT) in patients with CAD who were experiencing a major depressive episode was conducted. A significant antidepressant effect was noted for citalopram in comparison with placebo, but there was no demonstrable benefit of the psychotherapeutic intervention, IPT, over clinical management alone (23). All three of these SSRI trials showed a benefit to aggressively treating MDD post-MI. It is unclear if resolving depression improves morbidity and mortality or perhaps the SSRIs possess an independent morbidity-lowering factor. For example, most SSRIs carry FDA cautionary statements that increased bleeding and bruising may occur with use. Platelets interact with serotonin as part of the clotting process. Perhaps increasing CNS serotonin helps depression, but peripheral increases may decrease clotting and further MIs. This statement is theoretical in nature, but is worth future experimental analysis.

For patients who do not respond to SSRIs or have sexual dysfunction or want to stop smoking, bupropion may be a good alternative choice, although it is devoid of serotonin activity (24). Mirtazapine is thought to be safe for the heart, but because of its side effect of weight gain it has limited use in practice (25). Tricyclic antidepressants (TCAs) should not be used due to their association with adverse cardiovascular events (26).

Because of limited follow-up duration of the available studies above, the full effect of ADT on longitudinal cardiovascular mortality has not been completely investigated. Thus, it is not known whether treating depression improves cardiovascular outcomes, but ADT with SSRIs is generally safe, alleviates depression, and improves quality of life. Preliminary data suggest that screening cardiovascular patients for MDD is prudent, and aggressive treatment is warranted when MDD is diagnosed. The limited evidence base would suggest using SSRI as the first-line treatment. Where drug interactions are an issue, escitalopram and sertraline should be considered first. There is little data on selective norepinephrine reuptake inhibitor (SNRI) use, but it should be noted that desvenlafaxine and venlafaxine have likely the lowest p450 issues; the lowest protein issues, allowing less digoxin; and coumadin protein interactions, and the metabolite desvenlafaxine is primarily excreted in the urine, allowing for easier use in hepatically impaired patients.

DEPRESSION AND CANCER

MDD is a common but often ignored problem in patients with cancer. The stages of dying suggest that depression or despair may be normal or even needed to navigate the emotional stress of a terminal illness. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) may call this an adjustment disorder. Many clinicians and layperson might think it is "normal" to be depressed. Finally, it may be difficult for even astute clinicians to tell the difference between full MDD and an adjustment disorder. For example, after one's cancer diagnosis, a grief adjustment may settle in, not unlike a grief reaction

after the death of a loved one. The difficulty is to determine when normal grief turns into full MDD.

MDD can also coexist with other psychological complications in these patients, such as adjustment disorder, nonspecific distress, anxiety, and loss of self-esteem and functioning. Various studies have shown that the prevalence of MDD varies from 10% to 25% in patients with cancer (27) and from 6% to 32% in patients receiving palliative care (28). Understanding this is important as depression may lead to decreased survival time in patients with cancer (29). Cancer types highly associated with depression include oropharyngeal (22–57%), pancreatic (33–50%), breast (1.5–46%), and lung (11–44%). A lower prevalence of depression is reported in patients with other cancers, such as colon (13–25%), gynecological (12–23%), and lymphoma (8–19%) (30).

Factors that may be associated with an increased risk of depression include young age, a prior history of depression, and the presence of uncontrolled medical symptoms from the cancer. Having a depressed mood may interfere with a patient's coping, or even complying, with treatment regimens, thus creating a further barrier to dealing with the cancer. Many studies in breast cancer show the rates of psychosocial distress are high, and similar, across patients with both early and advanced stages, although the illness-related causes of distress are different. Also, in breast cancer, body image impairment from mastectomy and sexuality aftermath generates higher rates of mood disorders (31). Uncharacteristically, a majority of the studies in prior literature have reported no significant increase in mortality with comorbid depression (11). Very little has been done to specify whether or how psychological states may be involved in the risk of cancer. Some studies have shown that persons with allergies may be at decreased risk of cancer (32). The ambiguous relationship between stress and immune response was discussed in brief above.

Major depression is a treatable condition, even in persons who are terminally ill. Because depression treatments are usually relatively benign, experts recommend that clinicians have a low threshold for initiating treatment. The first step should be assessment and management of any patient with the diagnosis of cancer (33). Many women prior to childbirth are warned of postpartum blues and depression, and part of informed consent and many clinicians are routinely screening for depression in this population. It would make sense for those who deliver the cancer diagnosis also provide informed consent about "blues" or adjustment disorders and how these may progress to depression. This would increase treatment interventions and also allow patients to more easily discuss the potential arrival of MDD with their clinicians. In patients with persistent depression despite adequate pain control, antidepressants should also be initiated. Given data on neuropathic pain, use of SNRIs, or TCAs may be warranted here over SSRIs. Although no controlled clinical trials have evaluated the efficacy of combined interventions, most experts recommend an approach that combines supportive psychotherapy, patient and family education, and antidepressants (1). A therapeutic alliance between the primary caregiver and the patient is the most important factor for the success of any supportive psychotherapy. A few randomized controlled trials (RCTs) have also shown the efficacy of cognitive behavioral therapy (CBT) and existential therapies in patients with cancer (34). Although, there have been only a few trials of ADT in the setting of cancers (psychostimulants, SSRIs, and tricyclics), antidepressants can be used for treatment of depressed, terminally ill patients in whom

psychotherapy is not a viable option (35). Often those who are terminally ill and nearing death cannot attend therapy sessions on a weekly basis, making medications more necessary. The choice of antidepressant is governed by a decision on which drug is best suited to the individual patient. In a large community study, SSRIs were better tolerated and more likely to be continued than TCAs. Again, we would suggest using drugs with low p450 interactions (i.e., venlafaxine, desvenlafaxine, sertraline, escitalopram, mirtazapine). Mirtazapine is an interesting choice, which is usually demoted to second line as it has stand out remarkable weight gain, but in cachectic cancer patients it may be considered a worthwhile front-line drug.

Despite the fact that depression appears to be associated with numerous negative consequences, this disorder remains underdiagnosed and undertreated. Adequate recognition and treatment of depression in patients with cancer can enhance quality of life and help patients and families.

DEPRESSION AND STROKE

Depression commonly follows an ischemic cerebrovascular event, or stroke. Of the approximately 600,000 Americans who suffer from a stroke each year (500,000 new cases and 100,000 recurrences), only about 70% to 80% of patients survive the acute event. From the survivors, as many as 30% to 40% can suffer from depression either acutely within six months or subacutely up to the one to two years following the stroke. According to some studies, stroke survivors have a much greater chance of developing depressive symptoms even two or more years after index stroke regardless of functional disability, cerebrovascular risk factors, and past history of depression (35). Similar to patients diagnosed with cancer, clinicians and laypersons often expect stroke patients to be depressed. The greater the functional loss, we would expect more depression. The data above suggest that MDD may occur regardless of functional loss. An accurate diagnosis of depression in the immediate post-stroke period is difficult due to the high prevalence of sleep problems and fatigue these patients suffer from. In addition, stroke patients with frontal lobe involvement also frequently display emotional lability and/or apathy. This can easily masquerade as depression (36). Anatomically speaking, the more frontal a stroke is, the more likely depression will be to occur. Interestingly a few studies have shown that there is some connection between the development of emotional lability and subsequent depression (37). Theoretically, one could attempt to link up stroke damage to particular depressive symptoms, although this has not been studied. For example, a stroke in the dorsolateral prefrontal cortex may cause poor attention and concentration, or if this were to occur in the orbitofrontal areas, then more despondency and sadness may occur, etc.

MDD by itself has been recognized as an independent risk factor for the future development of stroke as demonstrated by several large studies (38). Depression not only increases relative risk for stroke but also leads to slowed recovery post-stroke (39). Functional recovery and ability post-stroke is likely dependent on early intervention in physical and occupational therapy. Despondent, amotivated, poorly concentrating depressed stroke patients are much less likely to adhere to the therapy that is needed to gain functionality back. This relationship is complicated by the fact that there is growing evidence to support an underlying vascular cause (small vessel ischemic disease) of

depression in the geriatric age group (40). In this chicken and egg situation, whether depression comes first versus the vascular/ischemic insult is difficult to clarify in most patients. In addition to an increased risk of a future stroke, stroke mortality is also increased if MDD is present (41) according to at least two large and several small studies.

In spite of a number of treatment options now available to successfully treat depression, there is growing evidence that depressive episodes that follow strokes are frequently either undiagnosed or undertreated, leading to not only needless suffering in the recovering patient but also to higher future risk of recurrence. As far as ADT choice, we would suggest using a non-noradrenergic agent, as norepinephrine can increase blood pressure, which is the highest risk factor for future strokes. SSRIs may be warranted over SNRIs, TCAs, bupropion, mirtazapine given this.

DEPRESSION AND MULTIPLE SCLEROSIS

The lifetime risk for depression in patients with multiple sclerosis (MS) has been estimated at greater than 50%. As depression is the most common psychiatric disturbance in MS, it has been the most studied. The basic phenomenology of depression in MS overlaps with that found in MDD, though irritability, frustration, and discouragement are more typical of depression in MS patients than feelings of guilt and low self-esteem (42). In addition, classic neurovegetative symptoms of depression, such as insomnia, appetite disturbance, and fatigue, may be equally attributable to the MS itself. In consultation psychiatry services when diagnosing depression, our usual approach is to include depressive symptoms regardless of origin, that is, whether fatigue is related to MDD or MS. Either way, the target symptoms of fatigue should be alleviated to improve quality of life.

The etiology of depression in MS is fairly complex, although a number of studies have indicated a connection to brain lesions and/or atrophy. Pujol et al. noted that hyperintense lesions localized to the arcuate fasciculus were associated with depressive symptoms in 45 patients assessed per Beck Depression Inventory findings (43). Another study that compared patients with MS with and without MDD found a connection between mood symptoms and the presence of superior frontal and superior parietal hypointense T1 images (44). Rabins et al. noted that brain atrophy, particularly lateral ventricular enlargement, is a predictor of depression in MS (45). Non-CNS factors that have been implicated in the development of depression include autoimmune and endocrine dysregulation. Studies have found associations between a lower number and percentage of CD8+ cells and a higher CD4/CD8 ratio in the blood. While depression is normally associated with a loss of negative feedback regulation of the hypothalamic-pituitary (HPA) axis, thereby leading to high cortisol levels that do not respond to a dexamethasone suppression, MS patients have exhibited even greater failure of suppression from this test (46).

Patients with MS and depression are also likely to have comorbid anxiety, fatigue, and cognitive impairment as well as an elevated risk for suicide. Common treatments for MS, including interferon β-1a and other disease-modifying drugs, may possibly increase the risk of depression. Recent studies, however, have called this long-held assumption into question. The Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) trial

examined patients from 9 countries and 22 treatment centers. Researchers found that pretreatment depressed mood was the best predictor of subsequent depressive symptoms, with no difference in depression across treatment versus placebo arms (47). A later study also found that depression is not a side effect of interferon β-1a when treating secondary progressive MS (48).

Given the vast impact on quality of life, treatment of depression is of great importance in MS. There is a paucity of well-designed, randomized, controlled treatment trials, however. Schiffer and Wineman conducted a double-blind, controlled trial, which found that TCAs (specifically desipramine) were more effective than placebo at treating symptoms (49). Open-label studies have examined SSRIs and found some treatment efficacy in these drugs as well. From a psychotherapy standpoint, treatments that involve adaptive coping skills (e.g., CBT) have proven helpful in some studies.

Much remains to be learned about the etiology and treatment of this debilitating illness. With depression rates as high as 50%, there is a pressing need for further research into this chronic disease.

DEPRESSION AND ARTHRITIS

Rheumatoid arthritis (RA) is a common debilitating disease of unknown, but likely autoimmune etiology that causes symmetric inflammation of the joint synovium. MDD also affects between 13% and 17% of patients with RA (50–52). It is estimated that MDD is two to three times as common in patients with RA as in the general population (53). Depression increases the burden of RA to the patient and society. Higher levels of depressive symptoms among people with arthritis are associated with greater risk of becoming work disabled, higher use of health services, and worse health outcomes overall compared with those who are not depressed (54). RA, especially, is often perceived to be due to psychological factors and stress. In common with other painful conditions, depression associated with RA is often considered to result from the experience of chronic pain, disability, and loss of function. Some studies have shown that the degree of depression varies in proportion to the level of pain. Correlation coefficients between pain and depression of approximately 0.4 have been found, which are significant (50,55,56).

Pain, fatigue, functional limitation, and social isolation are major risk factors for the development of depression and are often experienced by persons with arthritis. Factors that have been purported to be related to new onset of depression in RA patients include female gender, younger age at diagnosis (57), and personality traits such as low self-esteem, helplessness, and avoidant coping styles (58,59). Individuals vary greatly in their psychosocial acceptance of the diagnosis of RA, and poor adjustment to this diagnosis contributes to the onset of depressive symptoms (60). A large prospective study including over 1000 RA patients demonstrated that comorbid MDD is an independent predictor of mortality due to all causes in RA patients. RA patients with persistent or recurrent MDD were at least twice as likely to die than patients with no depression. The effect of depression persisted beyond the early years of the observation period, which suggested a true depression-mortality association (61).

Treatment should include both disease and pain management and adjunctive antidepressants or psychotherapy (62). Studies of psychological

interventions, such as CBT, have shown that they can play an important adjunctive role in both newly diagnosed and chronic RA (63,64).

DEPRESSION AND HYPERTENSION

The role of psychosocial factors, such as the "type A" behavior pattern, depressive symptoms, and anxiety, in the etiology of hypertension is supported by many epidemiological investigations (65).

Contrary to the above diseases, depression and risk of newly diagnosed hypertension may be inversely correlated. This may be due to the fact that depression may be associated with reductions in blood pressure as depression and/or anxiety resolves. Not only this, it has been found that physicians may be less likely to diagnose asymptomatic conditions, of which hypertension is one, in depressed patients as compared with nondepressed ones (3).

In the CARDIA study no independent association between depression or anxiety and 10-year incidence of hypertension was found, although depression categorized into three groups was positively associated with very high blood pressure, particularly among whites (66).

More often, as psychiatric clinicians we become worried with inducing hypertension in our depressed patients by way of using noradrenergic ADTs. Venlafaxine and desvenlafaxine have clear precautions but in our experience duloxetine, bupropion, desipramine, nortriptyline, and protryptiline are all noradrenergic and may act as pressor agents. In general we try to use SSRI in patients with very brittle hypertension, that is, if it took three to four antihypertensive medications to control blood pressure, but in ordinary well-controlled essential hypertension we have not had much of an issue with the SNRI.

CONCLUSIONS

As in medicine, the more comorbidity that exists, likely the worse outcomes for patients. This appears to be true, for the most part, where depression is concerned. Many MDD patients (>50%) will also have significant other axes I and II comorbidity as well, which further complicates our picture. Clinically, psychiatrists should be more astute about medical issues and common comorbidities. We should take better family medical as well as genetic histories. We should take an extensive past medical as well as psychiatric history, and finally, we should include a full medical review of systems as part of our initial evaluations. We should be in routine contact with our patient's primary care clinician to optimize treatment. These efforts should afford our patients better outcomes. Primary care, similarly, should strive to become better at diagnosing depression in the face of chronic medical illness. Second, much more aggressive medication management (full doses and full duration of SSRI and SNRI) should occur as the norm and not the exception. A collaborative approach would serve our patients and us well.

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13 Depression and Addiction

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INTRODUCTION

We should not assume that we know a lot about either depression or addiction. These illnesses are causing terrible morbidity and mortality despite the availability of treatments. This chapter reviews substantial evidence that both illnesses are due to a lack of relatedness. We need to learn more about why persons suffer from lack of relatedness, and what treaters can do about it. Psychotherapy may be the best treatment available. We prescribe medications to some patients with depression and addiction. While medications appear to improve outcomes, the mechanism of action is unclear. Prescribing for patients with depression and addiction varies substantially from that with nonaddicted patients, because of the danger of potentially abused mediations, and because of alterations in brain function caused by addictive drugs and addictive drinking of alcohol—especially damage to neural systems that initiate and preserve sleep.

The Prevalence and Comorbidity of Depression and Addiction

To discuss the comorbidity of depression and addiction, we must be able to define each. Already we are in a difficult position. Exactly what depression is, and exactly what addiction is, may not be definable with our current level of knowledge. For example, if depression is such a devastating illness, why then is it so prevalent? Why would not the genetic line of individuals with a predisposition to depression have died out millennia ago? How could depressed people survive prehistorical conditions? We must conclude that depression must have some functional use. And what exactly is addiction? Perhaps we could all agree that injecting heroin daily is addiction. But where do we draw the line on drinking? Is it daily drinking? Is gambling an addiction when there are serious consequences? What could the brain mechanism be? Could one be addicted to surfing the Internet, to exercise, or to watching television?

We would want to come up with answers that make empathic, intuitive sense, and also have some scientific basis. We have all seen people and patients with depression and with addiction. We have seen their suffering. We know that depression and addiction overlap. In the National Epidemiologic Survey on Alcoholism and Related Conditions, the prevalences of lifetime and 12-month major depressive disorder were 13% and 5%, respectively. Among subjects who had a lifetime diagnosis of major depressive disorder, the incidence of alcoholism (abuse or dependence) was 40% and drug addiction (abuse or dependence) was 17%. In addition, 30% of subjects with major depressive disorder were addicted to nicotine (1). Why would depression and addiction overlap?

Depressive episodes occur twice as often in women as in men (DSM-IV, p. 325) (2). What if access to alcohol and drugs did not exist? Would men have just as much depression? Apparently yes; in a study of 12,500 Amish people in whom alcoholism and drug abuse did not complicate the course of depressive

disorders because they are culturally prohibited, equal numbers of men and women suffered from major depressive disorder (3). One way to interpret this finding is that more women tend to tolerate distress without resorting to the use of alcohol and drugs to modulate their suffering, whereas men more frequently begin to self-medicate even before their distress can be diagnosed as a depressive disorder (4). Therefore, we may be observing two symptomatic constellations of an identical underlying problem. In this model we might find that women presenting for depression treatment were at risk for developing or being diagnosed with addiction, and men presenting for addiction treatment had undiagnosed depression.

The author fully admits that a caveat exists in the first paragraph in that there is not enough knowledge to be certain that the information below will hold up over time. In fact, the nature of psychiatry is such that we are constantly updating our thinking and treatment with new discoveries. In a common aspect related to depression, addiction also has to do with an inability to tolerate human relationships that are further articulated below.

In terms of defining depression and addiction, we will take two approaches. Similar to chapter 1, the first is to use the consensus of DSM-IV (2) as our most basic framework. Major depressive disorder is defined as one or more major depressive episodes in the absence of manic or hypomanic symptoms. DSM-IV differentiates a major depressive episode from a substance-induced episode. This differentiation is difficult for reasons that are discussed later, and many persons with a "substance-induced" episode go on to have "real" major depressive episodes during sobriety (5). One way to differentiate "abuse" and "dependence" in DSM-IV can be expressed as follows: in abuse the alcohol or drug use interferes with love and work; in dependence love and work interfere with use. A summary of the DSM-IV criteria for addiction amounts to "repeated harm from *X*," where "*X*" is alcohol or drug use behaviors.

The second approach to defining depression and addiction is to look conceptually at the nature of these disorders—how falling ill with either interferes with the social aspect of human life. In both depression and addiction, lack of relatedness is a central aspect of the illness.

Depression and Unrelatedness

What is the first thing that any baby does when it is separated from its parents? It screams bloody murder. It cries and demands and protests. Any parent hearing this sound feels compelled by their physiological response to run over and pick the child up. But what if one lived under conditions where there were predators lurking and the limited amount of food available meant that energetic protest by a lost child for an extended period might threaten predation or starvation? These conditions would favor an interior mechanism to shut off the crying so that predators could not locate the child, and energy was conserved. This response, depression, has strong evidence at both developmental and neurobiological levels (6).

Depressed patients typically have both childhood and adulthood difficulties in relatedness. The psychoanalytical concept regarding the lack of maternal care and the ensuing psychopathology was termed by Freud (7) "anaclitic depression." This lack of ability to depend on adequate parents has been understood as a central issue in the development of borderline personality

disorder (8). Maternal deprivation has been shown to be a major risk factor for the development of both depression and addiction (9).

Maternal deprivation has been modeled in animals such as rats. In classic experiments Nemeroff and coworkers (10) separated rat pups during a developmental period when they needed their mothers (days 2–14 of life). One group of pups was made to suffer a brief period (15 minutes) of separation. The response of the mother when these pups were returned was jubilant reunion. The mothers licked the pups more than other littermates (this is the rat equivalent of human hugging). All the attention made these pups resilient in later life. A second group of pups were forced to endure separation so long (three hours) that they were not recognized as part of the litter on their return. The mother bit them, stepped on them, and ignored them.

These abandoned rats after reaching adulthood had constantly high levels of the stress hormone corticotropin-releasing factor (CRF). This is exactly the same pattern seen in adult humans with depression (9). Moreover, the rats could be given paroxetine, which would normalize their CRF. When the paroxetine was discontinued, the CRF levels again rose to depression levels. Hence, Nemeroff was able to recreate the childhood conditions that give rise to depression in humans by using a laboratory animal.

There is an extensive literature showing that childhood adversity leads to adult depression (11). One would think that the obvious answer to treating depression in humans who have suffered childhood adversity would be to give antidepressants, that the addition of antidepressants to human relationships in the treatment of depression has to do with restoration of brain health so that the patient is able to use potential relationships, including one with a psychotherapist, to correct their ability to live in a social manner. The antidepressants help, the human relationships help, and the psychotherapy helps. For example, in one study of nefazodone alone, cognitive behavioral therapy alone, or a combination of both treatments showed a response rate measured by the Hamilton Rating Scale for depression (HRSD) of 55% for nefazodone, 52% for psychotherapy, and 85% for combined treatment (12). However, a reanalysis of the data where subjects who had been exposed to early-life traumata were separated from other subjects showed that the psychotherapy alone had identical outcomes to the treatment with nefazodone added to psychotherapy (13). Hence, as suggested by both Nemeroff and Freud, we may be grouping different types of illness into the same category, and naming it depression. The point here is to keep social relatedness in the forefront of thinking about depressed patients.

Addiction and Unrelatedness

What happens when an adolescent needs to grow up and leave his or her parents, and he or she experiences overwhelming separation anxiety? One solution is the adoption of an addictive behavior that makes the persons less anxious (14). The "addictive search" (15) terminates with an adolescent who is happily drinking alcoholically, using drugs, gambling, etc., and feels comfortable engaging in adult activities as long as he or she can stay related to the addiction that has a transitional object quality; the same kind of transitional object that might soothe an infant that experiences separation distress at a vulnerable period between six months and two years. The typical teenager with an addiction feels wonderful about having solved the problem of how to

separate from his or her parents and relate to his or her peers by using drugs or alcohol as a bridge. Formerly isolated and anxious, the teenager now knows that he or she belongs to the drug-using crowd (14). The addictive behavior is idealized (16) as a defense against his or her fear of the consequences of use.

However, as the adolescent gets older, the liabilities of the addictive behavior become more pronounced. Such persons become more ambivalent about their addiction as they get older; although rather than conscious ambivalence there is often addictive splitting. The addictive behavior may be consciously experienced as aversive one time and desperately desired at a later time. Splitting involves idealizing the addictive behavior as giving them a wonderful sense of relatedness, even while their addiction makes them unable to sustain relationships. Splitting gives a sense of omnipotent power even as their real abilities in the world diminish. Splitting gives a sense of independence even as they become more dependent on those around them in a hostile manner. And splitting feels like a rebellious separation, even as it makes establishment of an adult autonomous life less likely. Interpersonally, the splitting enables the addicted persons to retain their relationship with the addiction despite their professing to a treating person that they are done with the addiction (14,17).

Ideally, such a person would give up his or her dependence on the addictive behavior and instead shift his or her need for support to a person or persons ("depend on people, not drugs"). Shifting the dependence to one individual support person can be hard on that person, since all the hostility that was originally expressed by the relationship with the addictive behavior now must be contained within the new relationship (18). An alternative is to give up splitting, condemn the addictive behavior as uncontrollable, but "turn over" dependency to a "higher power" who is personified through the members of Alcoholics Anonymous (AA) or another 12-step organization via dependency on a sponsor and other group members. Newly sober patients or AA members are gradually detoxified from hostile relationships—the process of recovery. Actively addicted persons express anger indirectly via addictive behaviors, and the process of recovery from addiction includes the ability to set limits with the loving people around (19) rather than being superficially submissive and then ragefully uncontrollable. As the addicted persons heal, their recovery often takes the form of increasing spirituality, a sense of being related to many persons and important to people that one might not even know—such as a new sponsee at a meeting of AA.

Brain Mechanisms of Addiction

The impact of addictive drugs on the brain is one of the saddest and least appreciated aspects of medicine. Teenagers routinely provoke changes in their brains out of ignorance, changes that may never be reversed. Of course, the specific action of each drug leads to particular changes, but the common pathway of all addictive drugs is the shifts initiated in the ventral tegmental dopaminergic *seeking* system. This system is called seeking by its discoverer, Jaak Panksepp, to differentiate it from other motivational systems such as *rage*, *panic*, and *fear* (20). (As an example, the panic system is set off by separation; it is the system that initiates crying in the baby who wants its parents.) The seeking system is the system built into animals to provoke approach behaviors, originally toward natural incentives such as food, water, and sex (21).

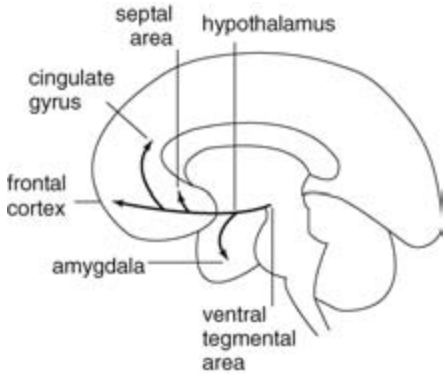

FIGURE 1 The seeking system.
Source: From Ref. 22.

Remarkably, there are only about 20 types of chemicals in the world that sensitize this system so that the animal looks for that chemical in its environment, but the list has all the familiars—nicotine, amphetamines, cocaine, alcohol, marijuana, benzodiazepines, opiates, phencyclidine, etc. (Fig. 1).

The use of any type of addictive drug provokes dopamine barrages from neurons with their nuclei in the ventral tegmental area of the midbrain to neurons in the nucleus accumbens shell. From here increased neural signals flow rostral, with important connections to amygdala, hippocampus, frontal areas, and cingulate gyrus. The higher areas communicate back to the ventral tegmentum and nucleus accumbens shell via glutamate, alerting the lower centers to the potential presence of addictive drugs. The specific sites of action of addictive drugs are now known for cocaine, amphetamines, nicotine, and opiates (Figs. 2 and 3).

This is the neural mechanism of "drug cues." Frontal areas (such as eye fields that orient visual scanning toward a desired stimulus), the hippocampus (identifying a spatial memory such as being in a neighborhood where drugs were bought), or the amygdala (such as having a feeling of anxiety about using drugs) detect the possible availability of a drug one is addicted to. This sets off intense dopamine-mediated signals with motor outputs that are experienced as craving and irresistible urges to move toward the possible source of the addictive drug. Another change in the seeking system is a tonic signal to look for drugs, a signal that is experienced at night as "drug dreams," the pathognomonic experience that one wakes up with a feeling that one just used or were just about to use drugs (25).

Food, water, and sex drives are modulated homeostatically. As consummatory behaviors that are evolutionarily preserved from creatures alive millions of years ago, the seeking system pathway from ventral tegmentum to nucleus accumbens runs through the hypothalamus where internal states, that is, satiety, are sensed and the drive for various needs is modulated (Fig. 4).

Humans have been able to procure psychoactive drugs that escape modulation and have an allostatic effect on brain systems. "Allostatic" means that there is no innate homeostatic mechanism to regulate the stimulus; the homeostatic detectors/regulators pictured in Figure 4 do not work. The brain is pushed into a range of functioning where it would never exist naturally.

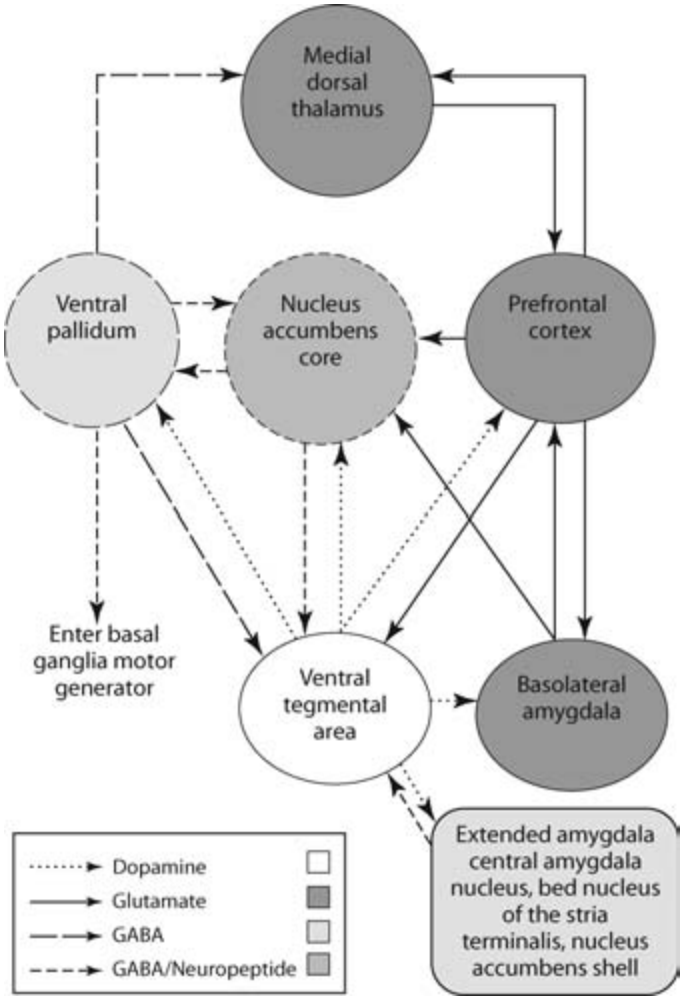

FIGURE 2 Neural circuit–mediating goal-directed behavior, including drug and alcohol seeking. *Source*: From Ref. 23.

Adaptations to allostatic changes include a stress response and various problematic changes that may be damaging to regulatory systems. For example, in response to the overwhelming dopaminergic surge provoked by cocaine's inhibition of the presynaptic reuptake transporter protein, the whole dopamine system becomes less active. This can be seen by looking in the retina, which uses dopamine as the neurotransmitter to indicate that light has impinged on neurons. Dopamine function in the retina, and presumably the whole brain, is substantially reduced after cocaine use (26). When the occupation of μ-opiate receptors by any one of the opioid drugs provokes intense stimulation, the brain makes changes that would never occur in nature (Fig. 5).

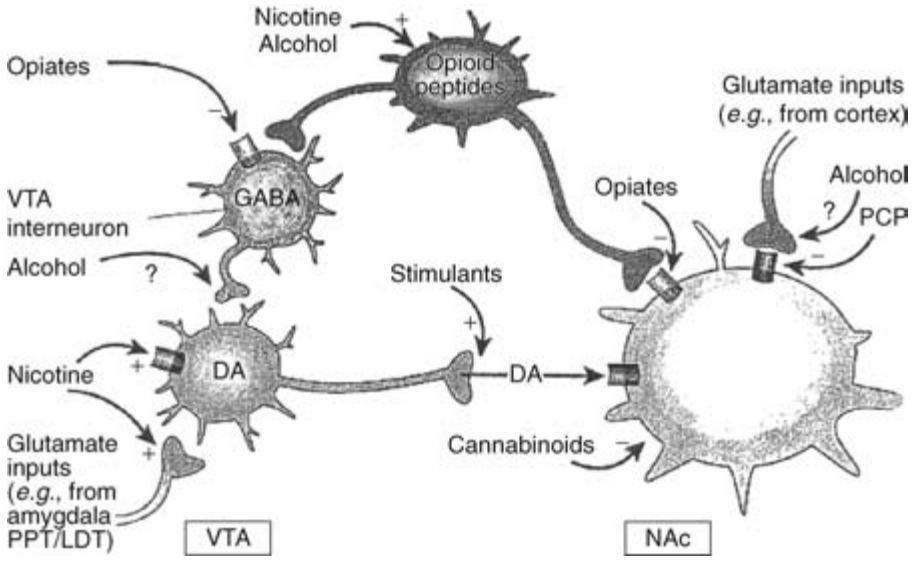

FIGURE 3 Actions of specific addictive drugs in the SEEKING system. *Source*: From Ref. 24.

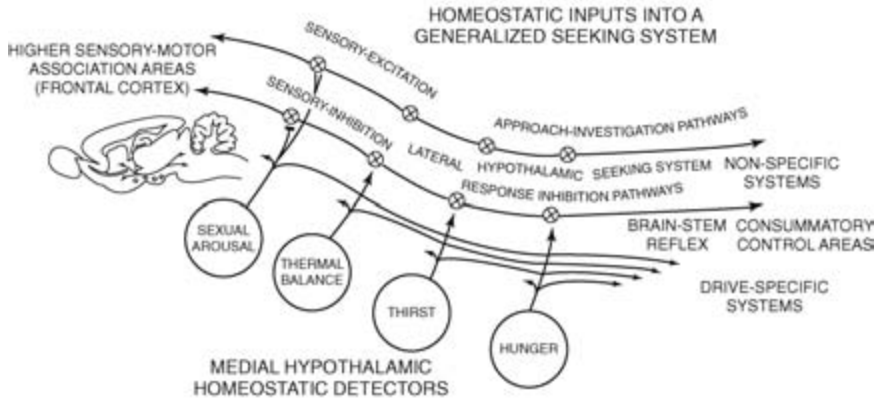

FIGURE 4 Input of natural incentives through the SEEKING system. *Source*: From Ref. 20.

Koob and Le Moal (27) call this the "a" process. The brain experiences intense and enduring stress resulting in high levels of CRF, and tries to get back to homeostatic functioning by instituting a "b" process. Opioids in particular cause an overshoot of functioning so that mood and pain syndromes result from drug exposure. For example, the average time normal controls were able to keep their forearm submerged in an ice-water bath (the "cold pressor test") was 65 seconds. The average time methadone-maintained opiate-addicted subjects were able to keep their forearms submerged was 15 seconds (28). This then brings up a question that we will return to later—are all the mood disorders we

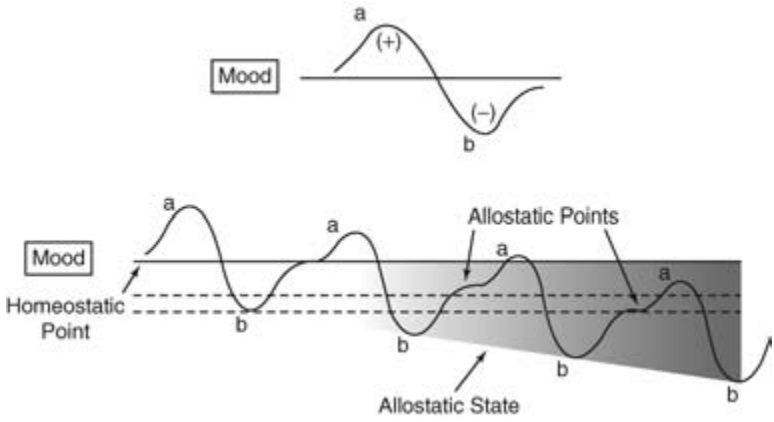

FIGURE 5 Deterioration of drug response to mood or pain as a result of the b process of allostatic compensation. *Source*: From Ref. 27.

see in addicted persons primary or secondary? Is it possible that some of the depressions we see in addicted patients are drug induced, a routine complication of addiction?

One would think that the systems that were changed by drug exposure and resulted in allostatic adaptations would reverse with abstinence. However, this is probably not true. Changes in sleep induced by cocaine only became worse with more time abstinent in subjects who were followed for 17 days after exposure (29). Hyperalgesia that was induced by opiate exposure persisted for months in abstinent subjects (30). Drug dreams have been documented to persist through five years of abstinence (22), and this author has anecdotally been told that one person with alcoholism still had drug dreams after 32 years of abstinence and one person with nicotine dependence still had drug dreams after 50 years of abstinence. Hence, the nature of exposure of the brain to addictive drugs is that there is a permanent change in the seekinG system. There may, in addition, be other permanent changes in sleep, pain tolerance, and mood, depending on the drug.

The destructive effects of drugs gradually make recovery less likely. Frontal damage may make addicted patients less able to restrain urges to respond to drug craving, and therefore help turn drug seeking into an automatic, unconstrained behavior (31). Behaviors that were initially organized with the cooperation of cortical areas can be reorganized as compulsive actions that are directed by the nucleus accumbens core (32). If the nucleus accumbens core organizes drug-seeking behavior, a late development of addiction, drug seeking then has become a pure subcortical behavior. Specific drugs have independent mechanisms of brain injury such as excitotoxicity, thiamine deficiency, and liver disease in alcoholism (33,34), hypoxic or anoxic brain injury from cocaine-induced arterial vasospasm (35), opiate-induced hypoxic brain injury during overdose, or less specifically understood cognitive deterioration after opiate exposure (36). We know that cognitively impaired patients are most likely to leave treatment and be intolerant of psychotherapy (37). Therefore, careful cognitive assessment of addicted patients is central to any evaluation.

Diagnosis of Depression in Addicted Patients

Withdrawal has overlapping symptoms with depression. Therefore, it is necessary to wait a certain amount of time before a diagnosis of depression is reliable. In one study of subjects who had been admitted to a dual-diagnosis hospital service while in alcohol withdrawal, it was found that scores on the HRSD were elevated for the first week and then normalized for most subjects. The remaining subpopulation was depressed persistently despite abstinence (38). In a study of 110 inpatients with alcohol, cocaine, or opiate dependence that were followed for a year, subsequent depression was equally likely among subjects with DSM-IV independent or substance-induced major depressive disorder that had been diagnosed initially (5).

On the other hand, in a study of subjects who were either started on antidepressants during their stay on an inpatient dual-diagnosis ward, or told to wait for a year before beginning on antidepressant treatment, 20% of the first group remained sober for a year, whereas all patients in the latter group relapsed within the first four months of the study (39). Hence, it is probably optimal to wait at least a week after alcoholic drinking to diagnose comorbid depression, but then to be aggressive about treatment. Depressed patients do not stay sober.

In practice, depression is probably overdiagnosed in addicted patients. We do not know which patients with depression have an autonomous depression that is likely to remain active whether patients enter a process of recovery or not, and which patients have some combination of an alcohol or drug-induced mood disorder that will remit with abstinence, possibly combined with a reactive depression that will also remit when the wreckage of a life disrupted by active use has been ameliorated by recovery. We do not know which patients would benefit by the Nemeroff-guided approach to address the need for psychotherapy and which patients might be helped by the addition of antidepressants.

Diagnosis of depression and specific provision of antidepressants to patients that antidepressants will help can be improved by the consideration of five types of information.

- Is there a family history of depression? This history makes autonomous depression more likely.
- Was there a premorbid (before addictive use) depression?
- During periods of abstinence, did the depression disappear or persist?
- What is the quality of depressive symptoms? Symptoms such as depressed mood, insomnia, or pain may be the result of recent drug use, whereas compulsive symptoms, mood-congruent psychotic symptoms, and weight loss during early abstinence are more likely to be due to autonomous depression.
- Is this a patient who has made many tries at sobriety and recurrently failed, as if there needs to be treatment of depression for them to tolerate and use interpersonal treatments?

In addition, because the shifts in depressive symptoms can be so complex, use of the HRSD is helpful in clinical practice (38). For example, patients can be initially assessed when they are acute, in danger, and not many days removed from alcohol or drug use. The HRSD can be repeated before initiating pharmacological treatments so that physician and patient can get a sense of whether

abstinence alone is effective in ameliorating the depression. One patient who had been resistant to stopping heroin found that his HRSD score of 20 fell to 0 with two weeks of abstinence. It was then clear to him that he was harming himself emotionally with his heroin use and he entered a sustained period of abstinence. One patient with cocaine dependence was persistently depressed during early sobriety, but her HRSD gradually declined. This slow decline over a three-month period reassured us that treatment with psychotherapy alone was probably right for her, and she also entered a sustained period of abstinence.

Another use of the HRSD is to document with addicted patients that non-mood-altering drugs have an effect. Some addicted patients are frustrated by the latency of onset of effect of antidepressants because they are accustomed to the emotional jolt and instant fix of addictive drugs. At times they complain that they do not feel anything when they take antidepressants. Giving such patients a copy of their HRSD can reassure them that the antidepressant is doing exactly what it is intended to do—make them well.

Choice of Pharmacological Agents in Treatment of Addicted Patients with Depression

Psychotropic medications used with depressed addicted patients vary considerably from the practice of general psychiatry because of the nature of addictive illness. Addicted patients are routinely excluded from clinical trials of patients with major depressive disorder (40) so the discussion below is admittedly less "evidence based" than it would be if sufficient evidence existed to modify these suggestions.

Use of stimulants, benzodiazepines, and antipsychotics with metabolic syndrome side effects are especially uncommon for the following reasons.

- Stimulants are often abused by addicted patients. Typically patients seen occasionally by a prescribing physician either sniff their stimulants or sell them (41). Stimulating antidepressants such as bupropion, desipramine, and atomoxetine take their place. Of course, if a psychiatrist is both prescribing and doing psychotherapy for a patient, there is freedom to prescribe stimulants because of the safety of being able to observe the effect of the patient over time.
- Benzodiazepines are a common cause of death for addicted patients because they get added to other sedating drugs leading to overdose (42). Their use with addicted patients is to be avoided because they are active in the seeking system. Benzodiazepines may not be especially addictive in the general population, but prescribing them for addicted patients may trigger relapse to the drugs from which the patient is trying to achieve sobriety. Once a person is addicted to one drug, they are predisposed to further addictions. Because addicted patients seek benzodiazepines, they may forcefully demand them from physicians, often claiming, "Nothing else works."
- Drugs such as quetiapine, risperidone, and olanzapine that increase cholesterol and predispose to type II diabetes interact with cigarette smoking; ubiquitous on addiction services, to make vascular complications such as myocardial infarction more likely. More alarming is a report that quetiapine has a heroin-like effect when sniffed or injected. It is mixed with cocaine to create "Q-ball," the quetiapine equivalent of the "speedball" that is made by mixing heroin and cocaine, and then injected (43).

Antidepressant treatment is also somewhat different with addicted patients.

- In general psychiatric practice, most patients are intolerant of the somnolence induced by trazodone. The severe insomnia induced by various addictive drugs, and the resistance to sedation that is created by addictive drugs, makes trazodone satisfactory to many patients when used in the range of 200 to 800 mg/day (44,45).
- Bupropion addresses a common triad seen with addicted patients—depression, attention-deficit hyperactivity disorder (ADHD), and nicotine dependence. Common side effects are increased libido and weight loss. Shame is a common problem for addicted persons. Treatment with a drug that would cause embarrassing side effects such as sexual dysfunction and weight gain would violate the fundamental rule of "do no harm." Somehow there is an impression that bupropion does not have antianxiety properties shared by all antidepressants, but this is not true (46), and it is just as effective as SSRIs (47).
- Tricyclic antidepressants are relatively infrequently used in general psychiatric practice because of the risk of suicide. Many addicted patients are eager to progress in their recovery and will tolerate severe depression without becoming suicidal. In situations where there is refractory depression, blood levels can be followed to insure compliance and to find the kind of dosing that is necessary for an individual patient. In the case where bupropion is not effective or not tolerated in the treatment of depression with comorbid ADHD, desipramine can be used with blood levels followed to check compliance and adjust dose optimally. It appears that desipramine is the most effective antidepressant for ADHD (48).

Treatment of comorbid anxiety is different also.

- There is an ingrained expectation for some addicted patients, based on the experience with addictive drugs, that for every problem there is a pill. The physician may want to ask about complaints such as "constant worry" and "racing thoughts." On closer examination such complaints often relate to the experience of being sober and noticing that problems of living lead to thinking about those problems. Patients who had been used to spending their nights being intoxicated find that they are sober and now spending their nights thinking about how to lead more productive lives. The AA slogan here is "living life on life's terms." Usually anxiety needs no pharmacological treatment.
- Blood pressure medications such as propranolol and clonidine ameliorate the hyperadrenergic state of post-acute withdrawal. They can be helpful for anxiety or insomnia during early abstinence (44,49). Propranolol 10 mg four times a day has utility as a placebo. One tells the patient, "Take this and sit quietly for 30 minutes when you are feeling upset so that the medication has a chance to work." After 30 minutes of serenity, the patient often feels calmer. Propranolol has a half-life of two hours, so does not build up with frequent use.
- Anticonvulsants such as gabapentin, valproic acid, and carbamazepine can help patients to tolerate treatment during early sobriety (49,50) or treat patients who have comorbid personality disorders and show their anxiety with hostile and aggressive behaviors.

- Antipsychotic medications function as "major tranquilizers." Since treatment of overwhelming anxiety tends to take place transiently, there is a negligible risk of tardive dyskinesia. Therefore, higher-potency first-generation antipsychotic drugs tend to be favored because they are inexpensive and do not produce a metabolic syndrome.

Addicted patients who attend 12-step meetings sometimes worry that they should not be taking medications for depression because they want to be "drug free." Sometimes they may quote the AA slogan that relates to prescription drug abuse, "A drug is a drug." These patients can be reassured that having addiction does not make one immune from any other illness, and that just as a sober person with diabetes might have to take insulin, a sober person with depression might have to take antidepressant medication. AA is aware of this problem. Some of the physicians who are AA members wrote the pamphlet, "The AA Member and Medication." Its two central points are as follows:

1. Go to doctors who understand addiction.
2. Tell your doctor that you have addiction.

CONCLUSION

Returning to the introductory theme, although we may understand the nature of both depression and addiction more in the future, the current goal of treatment is to have patients move toward a state of relatedness. With comorbid depression, especially with a history of childhood abuse or neglect, psychotherapy may be the treatment of choice. If pharmacological agents are used, the theme of relatedness should be continued through in prescribing.

Medications can be thought of as dulling or promoting relatedness. The nature of all drugs of abuse is that they dull relatedness. Benzodiazepines and opioids would be the main prescribed medication groups that also dull relatedness. Medications such as stimulants and quetiapine may be abused rather than used for recovery. The above approach to pharmacology involves treatments for depression and related ADHD or anxiety that increase the capacity of the patient to be related and to use psychotherapy, addiction counseling, or 12-step meetings.

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14 Treating Depression and Psychosis

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INTRODUCTION

Psychotic depression (major depression with psychotic features, delusional depression) is a serious illness during which a person suffers from the dangerous combination of depressed mood and psychosis; with the psychosis commonly manifesting itself as nihilistic-type delusions, or that bad things are about to happen. While psychotic depression is treatable if recognized, the diagnosis is frequently missed, which can lead to the prescription of ineffective treatments and unfortunate outcomes. Recent data from the National Institute of Mental Health (NIMH) Study of the Pharmacotherapy of Psychotic Depression (STOP-PD) suggest that the diagnosis is indeed often missed in both the emergency room and inpatient hospital settings (1). A further complication when treating psychotic depression is that no medications are approved by the Food and Drug Administration (FDA) for the treatment of this specific disorder, leaving the clinicians to base their decisions regarding patient treatment on only a very few studies published in the medical literature.

EPIDEMIOLOGY

Epidemiological studies of the prevalence of psychotic depression in the community indicate that it afflicts approximately 4 per 1000 people in the general population, although the community rates in people older than 60 have been reported to be higher. In a study of 18,980 people aged 15 to 100 years who were representatives of the general populations of several European countries, the prevalence of psychotic depression was 4 per 1000 people (2). In people older than 60, the prevalence of psychotic depression in the community is higher, between 14 and 30 per 1000 (3,4). In a Finnish community sample of people older than 60, the rate of psychotic depression was found to be 12 per 1000 in women and 6 per 1000 in men (5).

In samples of patients with major depression, the rates of psychotic depression are considerably higher. In a European study of patients who met criteria for major depression, 18.5% of them also fulfilled criteria for major depressive episode with psychotic features. In the United States, in the Epidemiologic Catchment Area Study (6), 14.7% of patients who met criteria for major depression had a history of psychotic features.

BIOLOGY

There exists considerable evidence from studies of the hypothalamic-pituitary-adrenal (HPA) axis, dopaminergic activity, enzyme studies, brain imaging, electroencephalographic sleep profiles, growth hormone (GH) response after administration of growth hormone–releasing hormone (GHRH), and measures of serotonergic function that point to distinct biological abnormalities in

psychotic depression as compared with nonpsychotic depression (7). Measures of HPA activity and sleep studies may be clinically useful in differentiating schizophrenic spectrum disorders from psychotic depression as these two disorders differ significantly in HPA axis activity and sleep study measurements. For a recent review of the biology of psychotic depression see Ref. 7.

DIAGNOSIS

According to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (8), one cannot make the diagnosis of psychotic depression unless the presence of delusions or hallucinations occurs in the context of a major depressive episode. However, psychotic depression is often not diagnosed accurately because the psychosis may be subtle, intermittent, or concealed, leading to a misdiagnosis of nonpsychotic depression (9). Improperly diagnosing a patient as having a psychotic disorder such as schizophrenia or failing to recognize psychotic features of a major depressive episode will defer the use of effective treatment modalities. Recent data from the NIMH STOP-PD (10) suggest that suboptimal treatment of psychotic depression is often occurring.

The detection of delusions and hallucinations is often difficult in patients with psychotic depression because the patients are frequently paranoid and suspicious and can be concerned that others will think they are "crazy" (9), and consequently, they have a tendency to keep their psychotic thoughts to themselves. Recent data from the NIMH STOP-PD indicate that clinicians frequently miss the diagnosis of psychotic depression, in large part because of a lack of recognition of the psychotic features (1). In this study, 27% of 130 diagnoses among a well-characterized sample of patients with a research diagnosis of psychotic depression were initially incorrectly diagnosed. Psychotic depression was most commonly misdiagnosed as major depressive disorder without psychotic features, depression not otherwise specified (NOS), or mood disorder NOS (1).

Several groups have reported that patients with psychotic depression demonstrate a more frequent and severe psychomotor disturbance (either retardation or agitation) than do nonpsychotic depressed patients (11–16). Patients with psychotic depression, when compared with nonpsychotic depressed patients, have also been reported to exhibit more pronounced paranoid symptoms (12,13), cognitive impairment (17–23), hopelessness (13), hypochondriasis (11,14), anxiety (14,16), early insomnia (12,13), middle insomnia (12), and constipation (24). Patients with psychotic depression also do not show a diurnal variation in mood compared with endogenously depressed nonpsychotic patients (24).

COURSE OF PSYCHOTIC DEPRESSION

In general, patients with psychotic depression take longer to recover and return to their baseline level of functioning than patients who suffer from nonpsychotic depression. Patients with psychotic depression (when compared with patients with nonpsychotic depression) exhibit increased use of services, greater disability, and poorer clinical course at short-term follow-up (25,26). Patients with psychotic depression also have higher rates of suicide and suicide attempts than do patients with nonpsychotic depression.

Psychotic depression tends to be a more recurrent illness than nonpsychotic depression. A study examining rehospitalization after first admission found that patients with psychotic depression were readmitted 45% sooner than patients

with nonpsychotic depression (27). Compared with nonpsychotic depression, patients with psychotic depression also exhibit more frequent relapses or recurrences (4,9,12,15,28–35), although not all studies are in agreement (36,37).

Once a patient has had an episode of psychotic depression, the risk of having psychotic features during future episodes of depression is substantial. Recurrence of psychotic features in major depressive disorder has been most extensively examined in an eight-year follow-up study of 424 patients with major depression (38). Patients who had been diagnosed with psychotic depression at intake had 4- to 15-fold higher risks of being psychotic during subsequent episodes of depression. Aronson and colleagues, reporting on a sample of patients with psychotic depression, observed a striking 86.5% relapse rate into depression over 32 months with almost all the relapses including psychotic features, with the majority of relapses (82.5%) occurring within the first year following discharge (28). Another study found that recurrence of psychosis (judged either retrospectively or prospectively) had occurred or did eventually occur in 92% of patients with psychotic depression (32). However, when compared with patients with schizophrenia, patients with psychotic depression were less likely to have delusional symptoms on three separate follow-ups (39).

Several studies have demonstrated residual social and occupational impairment in patients with psychotic depression despite improvement in psychotic and depressive symptoms at 1- (26), 5- (40), and 10-year follow-up (31), but a 40-year follow-up study found no consistent trends distinguishing psychotic depression from nonpsychotic depression on marital, occupational, residential, or symptomatic outcome ratings (41). The social and occupational impairment has been hypothesized to be secondary to subtle cognitive deficits associated with the higher cortisol levels frequently observed in patients with psychotic depression (26,42).

Patients with psychotic depression also have higher mortality rates from medical causes in addition to an increased risk of suicide (see section "Suicide Risk in Psychotic Depression"). In a 15-year follow-up of patients with psychotic and nonpsychotic depression (43), the mortality rate for subjects with psychotic depression was significantly greater (41%) than that for those with a diagnosis of nonpsychotic depression (20%). The higher mortality among patients with psychotic depression was not explained by a higher number of suicides, as most of the deaths (88%) were from medical causes.

SUICIDE RISK IN PSYCHOTIC DEPRESSION

The symptom profile of patients who suffer from psychotic depression makes suicide a serious concern: The person is suffering from severe depressive symptoms and, in addition, often has nihilistic-type delusions. Studies have generally observed (although there is not uniform agreement) that patients with psychotic depression have higher rates of completed suicide and suicide attempts than patients with nonpsychotic depression and tend to use more violent means.

The risk for suicide in psychotic depression has been reported to be 5.3 times higher than in nonpsychotic depression (44). This finding was based on a retrospective study of patients who committed suicide while hospitalized in an inpatient unit over a 25-year period. Robins (45), in a psychological autopsy study of 134 suicides that occurred in the 1950s, reported that 15.9% of the suicide victims with affective disorder had psychotic symptoms. The study did

not separate patients with unipolar disorder from bipolar disorder. In another psychological autopsy study, Isometsä and colleagues (46) reported that patients with psychotic depression were more likely to use violent means of suicide than patients with nonpsychotic depression (88% vs. 59%, $p = 0.03$). In contrast, several outpatient studies of patients originally hospitalized in an inpatient unit observed no increase in risk for patients with psychotic depression (41,47,48).

Risk of suicide attempts varies considerably from study to study, from increases of 2.6-fold (49) to no increase in risk (50). In a study of inpatients, Nelson and colleagues (51) reported an increased risk of suicidal ideation in patients with psychotic depression compared with patients with nonpsychotic depression. Miller and Chabrier (52), also in a study of inpatients, found that the risk of a suicide attempt was 1.5 times higher in psychotic versus nonpsychotic depressed patients, although the difference was not statistically significant. In the Epidemiologic Catchment Area Study, patients with psychotic depression had a greater number of attempted suicides and lifetime hospitalizations than nonpsychotic depressed patients (6). Several other studies (49,53,54) have observed that patients with psychotic depression had a greater risk for suicide attempts and/or suicidal ideation than nonpsychotic depressed patients. A study in the geriatric population did not find a difference between psychotic and nonpsychotic depressed patients (50).

Two studies (46,49) reported that patients with psychotic depression are more likely to use violent methods of suicide than nonpsychotic depressed patients, but others (50) have not found psychotic depression patients to have an increased risk of using violent methods. This may in part be age related, since the Lykouras sample (50) assessed a geriatric population, while in the other two studies the subjects were considerably younger (46,49).

TREATMENT OF PSYCHOTIC DEPRESSION

The American Psychiatric Association (APA) Practice Guidelines for the Treatment of Patients with Major Depression (2000) recommend, with substantial clinical confidence, the use of either electroconvulsive therapy (ECT) or the combination of an antipsychotic and an antidepressant for the treatment of psychotic depression. However, despite these recommendations, recent data have shown that only 5% of patients with psychotic depression receive an adequate combination of an antidepressant and an antipsychotic medication (10). These findings show little change from a study published a decade earlier, which also reported inadequate dose and duration of medication treatment prescribed to patients with psychotic depression (55).

The decision whether to treat the patient who suffers from psychotic depression with ECT or medications is complicated, and the decision depends to a large extent on the clinical situation and personal preferences of the patient. The literature on the relative efficacy of ECT compared with pharmacotherapies is limited by a lack of prospective, controlled trials. It is difficult to draw broad conclusions from meta-analyses that compared the efficacy of ECT with pharmacotherapy because the ECT treatment was often compared with several different combinations of medications, at varying doses, and for different periods of time (56).

Although some would argue that ECT is more efficacious and works faster than medications, there is a high relapse rate after its successful administration

(35,57). The use of ECT has been limited by a number of considerations, including (*i*) a large number of patients and their relatives preferring pharmacologic treatment because they find both the idea and experience of ECT, and the possible side effects of confusion and memory disruption (58), unacceptable (8,59,60); (*ii*) issues of accessibility (61); and (*iii*) the cost of ECT (62). ECT is often used as a first-line treatment in certain clinical situations such as life-threatening symptoms (e.g., severe suicidal ideation, poor nourishment), a history of previous good response to ECT, or in an older patient (59). Minority ethnic groups, patients with low incomes, and those residing in rural areas are less likely to receive ECT during a psychiatric hospitalization (62).

In a review of 17 prospective and retrospective studies comprising 597 patients with psychotic depression by Kroessler in 1985 (63), response rates reported were 82% for ECT and 77% for the combination of a tricyclic antidepressant (TCA) and antipsychotic, with considerably lower response rates of 51% and 34% for antidepressant monotherapy or antipsychotic monotherapy, respectively. A second larger meta-analysis, which included data from 44 prospective and retrospective studies published between 1959 and 1988 (60), found that ECT was significantly more effective than TCA alone, with effect sizes of 2.30 and 1.16, respectively. The combination of an antidepressant and antipsychotic was found to have an intermediate effect size of 1.56, which was not significantly different from the other two groups (60). The early initiation of ECT within five days of admission has been reported to shorten lengths of stay and reduces treatment costs (62), whereas hospital treatment with ECT is associated with longer lengths of stay when treatment is not instituted rapidly (62,64,65).

Some studies suggest that ECT may be even more effective for psychotic depression than for nonpsychotic depression. An open-label retrospective study of response to an acute course of unilateral or bilateral ECT in 30 patients with unipolar psychotic depression compared with 36 patients with unipolar nonpsychotic depression yielded response rates of 83% for the psychotic group compared with 58% for patients without psychosis [with response defined as a score of <10 on the 17-item Hamilton Rating Scale for Depression (HAMD)] (66). In a larger prospective study (67) of the response to an acute course of bilateral ECT in 77 patients with unipolar psychotic depression compared with 176 patients with unipolar nonpsychotic depression, the rates of remission were 95% for the patients with psychotic depression and 83% for the nonpsychotic group, with remission rigorously defined as a score <10 on the 24-item HAMD measured after each of two consecutive visits and a decrease of >60% from initial scores. Improvement in symptom ratings on the HAMD was of a greater magnitude and tended to be more rapid in the patients with psychotic depression compared with those without psychosis. In a meta-analysis of studies published between 1978 and 2001, ECT was more efficacious for patients with psychotic depression than depressed patients without psychosis (68). Finally, in a retrospective review of the records of 55 inpatients with major depression in the Netherlands, 92% of patients with psychotic depression achieved a 50% reduction in their HAMD score compared with 55% of nonpsychotic depressed patients ($p = 0.002$). Fifty-eight percent of patients with psychotic depression achieved a HAMD score of ≤ 7, compared with 24% of the patients with nonpsychotic depression ($p = 0.01$) (69).

However, in clinical practice in the community, much lower ECT remission rates have been reported than in the clinical trials of ECT (70). For example,

the intent-to-treat remission rates from a large cohort of adults treated with ECT in community facilities were in the range of 30% to 47% (70). The low rates of remission are of particular concern, given the poor outcomes of patients who do not remit with ECT (70). The low remission rates in community practice might be explained by the fact that patients with comorbid psychiatric and medical conditions (that are associated with poorer ECT outcome) might represent a larger proportion of the clinical population than the patients studied in clinical trials of ECT (70).

The APA Guidelines for the pharmacotherapy of psychotic depression, initially published in 1993, were based in large part, on two meta-analyses (63,71). The studies reported that the response rate of patients with psychotic depression to TCA monotherapy was less than 40% compared with 70% to 80% response rates of those treated with a combination of a TCA and an antipsychotic medication. However, of the 21 studies included in these two meta-analyses, only one was a randomized clinical trial conducted under double-blind controlled conditions with only 51 subjects (16–18 per cell) and no placebo control (72). The Spiker study (72) compared the combination of amitriptyline and perphenazine with amitriptyline alone and perphenazine alone in the treatment of patients with psychotic depression over a five-week period. Using a 50% reduction in HAMD and Brief Psychiatric Rating Scale (BPRS) total scores and a final HAMD score of less than 12 as response criteria, 14 of 18 patients (78%) treated with the combination responded, in contrast to 7 of 17 patients (41%) treated with amitriptyline alone and 3 of 16 patients (19%) treated with perphenazine alone. Seven of the 13 patients who failed to respond to perphenazine were not psychotic at the completion of the study but were still depressed. In this study, the mean doses of both amitriptyline (170 + 45.5 mg/day) and perphenazine (55 + 17 mg/day) were high, in particular when considering the drug-drug interaction between TCAs and perphenazine (TCAs tend to slow the metabolism of perphenazine, resulting in higher TCA plasma levels.).

Anton and Burch (1990) (73) subsequently conducted a randomized, double-blind investigation that explored whether the efficacy of the combination of amitriptyline plus perphenazine could be matched by monotherapy with amoxapine, an antidepressant derivative of the antipsychotic medication loxapine, with dopamine antagonist activity. Using a 50% reduction in HAMD score as criterion for response yielded response rates of 71% and 81% for amoxapine and amitriptyline plus perphenazine, respectively. Extrapyramidal symptoms were significantly more frequent in the amitriptyline plus perphenazine group than in the amoxapine-treated patients.

Since the 1993 APA Guidelines were published, there have been several large prospective studies of the medication treatment of patients with psychotic depression. In two large randomized controlled trials (74), a combination of the selective serotonin reuptake inhibitor (SSRI) fluoxetine plus the second-generation antipsychotic olanzapine was compared with olanzapine monotherapy or placebo in 229 hospitalized patients with psychotic depression. In both studies, patients were randomized to placebo, olanzapine (mean doses: 11.9 and 14.0 mg/day) plus placebo or olanzapine (mean doses: 12.4 and 13.9 mg/day) plus fluoxetine (mean doses: 23.5 and 22.6 mg/day) and followed for eight weeks. The first trial showed a reduction in HAMD score that was statistically greater in the combination group than in the olanzapine monotherapy group or the placebo group throughout the eight weeks. The second trial failed to reveal any

statistically significant differences between the three treatment groups except for the HAMD score in the combination group, which was statistically lower than the placebo group at the end of week 1. However, there were several aspects of the study design that were biased against the combination of fluoxetine and olanzapine. First, the study was powered to show a difference between olanzapine monotherapy and placebo and not the combination therapy, resulting in a small sample size in the combination group, which limited statistical power. Additionally, the study design limited fluoxetine dosing according to olanzapine dosing, such that most subjects received only a starting dose of fluoxetine (20 mg/day). It is plausible that if higher doses of fluoxetine had been used, it could have produced greater reductions in depressive symptoms or higher response and remission rates.

Wijkstra and colleagues (75) reported on a double-blind, randomized, controlled study of 122 hospitalized patients (aged 18–65 years) with psychotic depression at eight sites in the Netherlands. The patients were treated for seven weeks with imipramine ($n = 42$), venlafaxine ($n = 39$), or the combination of venlafaxine and quetiapine ($n = 41$). Dosages used were imipramine (dose adjusted to adequate plasma levels of 200–300 ng/mL), venlafaxine (maximum 375 mg/day), or venlafaxine-quetiapine combination (maximum 375 mg/day and 600 mg/day) respectively. The primary outcome measure was a response on the HAMD ($\geq$50% decrease, and final score $\leq$14). Remission was defined as a final HAMD ≤ 7. Response rates for imipramine, venlafaxine, and venlafaxine-quetiapine combination were 22 of 42 (52.4%), 13 of 39 (33.3%), and 27 of 41 (65.9%), respectively. For the primary outcome measure of response, the venlafaxine-quetiapine combination was statistically significantly more effective than venlafaxine; there were no statistically significant differences in the response rates between venlafaxine-quetiapine combination and imipramine or between imipramine and venlafaxine. Remission rates for the venlafaxine-quetiapine combination (17/41, 41.5%) were statistically significantly more effective than imipramine (9/42, 21.4%), with no statistically significant difference compared with venlafaxine (11/39, 28.2%) and no significant difference between imipramine and venlafaxine. The authors concluded that the combination of venlafaxine and quetiapine was more effective than venlafaxine alone on the primary outcome measure (response) and was well tolerated (75).

The recently completed NIMH STOP-PD study reported results that indicated that the combination of an antidepressant and an atypical antipsychotic medication was more efficacious than monotherapy with the atypical antipsychotic alone (76). The study included 259 subjects with psychotic depression, 142 subjects aged 60 years or older and 117 younger than 60 years. One hundred twenty-nine subjects were randomized to combination treatment and 130 to olanzapine plus placebo. Remission was defined as an HAMD score of $\leq$10 at two consecutive assessments without delusions, as classified by a schedule for affective disorders and schizophrenia delusion severity score of 1 at the second assessment when the two-week HAMD depression remission criterion was met. Subjects who achieved an HAMD score of $\leq$10 for the first time at week 12 were assessed again at week 13 to determine whether the two-week duration criterion for remission was met. The daily dosages of medications in the STOP-PD study were as follows: (*i*) initial doses of 50 mg sertraline/placebo and 5 mg of olanzapine as tolerated (frail elderly subjects initially received 25 mg of sertraline/placebo and 2.5 mg of olanzapine); (*ii*) increase the dosage of

sertraline/placebo by 50 mg/day and of olanzapine by 5 mg/day every three days as tolerated; (*iii*) attempt to achieve minimum doses of 100mg/day of sertraline/placebo and 10 mg/day of olanzapine by the end of week 1; (*iv*) increase doses to 150 mg/day of sertraline or placebo and 15 mg/day of olanzapine during week 2; and (*v*) allow doses of 200 mg/day of sertraline/placebo and 20 mg/day of olanzapine for residual symptoms beginning in week 3.

The results of the STOP-PD study (76) indicated that 67% of the study completers who received the olanzapine-sertraline combination achieved remission by week 12, compared with only 49% of study completers who received olanzapine monotherapy ($\chi 2 = 10.42$, df =1, $p = 0.002$). An analysis of all randomly assigned subjects found that the combination of olanzapine plus sertraline was associated with a greater frequency of remission (42% of 129 subjects) than was olanzapine monotherapy (24% of 130 subjects) ($\chi 2 = 9.53$, df = 1, $p = 0.002$). Remission rates in the young adult and geriatric samples were comparable.

In summary, four combinations of antidepressant plus antipsychotic medications have been studied in randomized controlled clinical trials of patients with psychotic depression and have been shown to be effective: sertraline plus olanzapine (259 subjects) (76), fluoxetine plus olanzapine (249 subjects) (74), venlafaxine plus quetiapine (122 subjects) (75), and amitriptyline plus perphenazine (51 subjects) (72).

There exists a small literature on augmenting the antidepressant-antipsychotic combination in psychotic depression. In three, small uncontrolled studies, lithium augmentation of the antidepressant/antipsychotic combination appeared to add additional efficacy, particularly in bipolar patients. In the first study, lithium augmentation of a TCA and an older typical antipsychotic medication were shown to be efficacious for psychotic depression (77). In a retrospective chart review of psychotic depression patients who were refractory to treatment with desipramine plus perphenazine or haloperidol (78), 8 of 9 patients with bipolar psychotic depression, but only 3 of 12 with unipolar psychotic depression, recovered when 600 to 1200 mg/day of lithium was added (Fisher's Exact Test, $p = .003$). Finally, in a study (79) of eight patients who did not respond to five weeks of treatment with the combination of fluoxetine and perphenazine, three of three patients with bipolar psychotic depression responded to lithium augmentation, in contrast to none of five unipolar psychotic depression patients ($p < 0.01$). The use of other augmentation strategies or the use of lithium augmentation with other combinations of antidepressant and antipsychotic medications has not been studied.

Finally, several algorithms have recently been proposed, incorporating the current evidence base, to help guide the clinician in the use of somatic treatments for psychotic depression (7,80).

TREATMENT-REFRACTORY PATIENTS

If a patient with psychotic depression does not respond to either an adequate trial of the combination of an antidepressant plus antipsychotic medication or ECT, it is important to ascertain whether the patient has had adequate treatment. If the patient received pharmacotherapy, it is important to check whether the doses of medication received and the duration of treatment were adequate. In fact, recent data have shown only 5% of patients with psychotic depression receive adequate dosages of an antidepressant and an antipsychotic (10). These findings show a persisting low rate of adequate treatment of psychotic

depression and little change from a study published a decade earlier, which also reported inadequate medication treatment of patients with psychotic depression (55). Patients were often prescribed inadequate doses of the antidepressant, the antipsychotic, or both.

It is also important to check to be sure that the medication trials were of a sufficient duration. To date, the largest studies of the medication treatment of psychotic depression (74,76) were for 8 and 12 weeks, respectively. Given that patients with psychotic depression may respond more slowly to antidepressant therapy than do patients with nonpsychotic depression (81), it may be helpful to continue a treatment-refractory patient with psychotic depression on the medications for a longer duration if this is clinically possible.

If the patient with psychotic depression was prescribed ECT, whether or not the course of ECT was adequate should be determined. Unfortunately, what constitutes an adequate trial of ECT cannot be precisely defined. A thorough review of the number of treatments received and whether they were unilateral or bilateral should be undertaken by obtaining the medical records from the facility where the ECT treatments were rendered. A retrial of ECT with a greater number of treatments and with more bilateral (than unilateral) treatments than the patient received previously may be indicated.

CONTINUATION AND MAINTENANCE TREATMENT

Determining the optimal continuation and maintenance therapy for psychotic depression is of special concern because of the high rate of relapse observed in naturalistic follow-up studies of psychotic depression (33), including relapse after ECT (28,57,82). Other concerns include high mortality rates (33,43), a high risk of extrapyramidal symptoms and tardive dyskinesia with first-generation antipsychotics (83), increased use of health care services (6), and a high rate of disability (6).

There is only one published randomized controlled trial of continuation pharmacotherapy for psychotic depression (84). In this study, the benefits and risks of combination pharmacotherapy with nortriptyline or sertraline plus perphenazine were compared with those of antidepressant monotherapy with nortriptyline or sertraline during a 26-week period in 28 older patients with psychotic depression who had remitted after being treated with ECT. Overall, 25% of patients relapsed during the 26-week trial, 33% in the combination therapy group, and 15% in the monotherapy group. The difference was not statistically significant because of the small sample size. Patients in the combination group were more likely to develop medication side effects, including a 43% incidence of tardive dyskinesia after six months of perphenazine treatment, even though none of the subjects had been exposed to prolonged antipsychotic treatment before entering the study.

In an open-label maintenance study, Rothschild and Duval (2003) (85) assessed the effect of discontinuing the antipsychotic medication in patients with psychotic depression. Thirty patients with the diagnoses of unipolar major depression with psychotic features who responded to the combination of fluoxetine and perphenazine were studied. If the patient was stable for four months on the combination, the patient was then gradually tapered off the perphenazine. Impending relapse was defined as any of the following: (*i*) symptoms meeting DSM-IV criteria for major depression (with or without

psychotic features), or (*ii*) a total score of ≥17 on the HAMD, or (*iii*) the presence of any psychotic symptoms. After tapering off the perphenazine after four months of treatment with fluoxetine and perphenazine, 22 of the 30 patients (73%) did not exhibit signs of relapse over the next 11 months while remaining on fluoxetine monotherapy. Patients who showed signs of relapse after antipsychotic taper were more likely to have had a longer duration of the current episode, a history of more frequent past episodes, and were more likely to be younger (younger than 30 years).

In another open-label maintenance study, Flint and Rifat (59) followed a group of patients older than 60 years with major depression with and without psychotic features for two years after remission of their index episode. The 68 patients with nonpsychotic depression were maintained on the treatment they had responded to in the acute phase (i.e., a therapeutic dose of nortriptyline with or without lithium augmentation), whereas 15 of the 19 patients in the psychotic depression group were treated with ECT and then switched to nortriptyline. (The four patients who declined ECT were treated with nortriptyline and perphenazine, and two of them needed further augmentation with lithium.) For patients who were treated acutely with perphenazine, the antipsychotic was discontinued by tapering the dose during a four-week period starting 16 weeks after the start of remission. Patients with psychotic depression were significantly more likely to suffer a relapse or a recurrence than the nonpsychotic group (47% vs. 15%, respectively, $p = 0.005$).

Studies have indicated that there is often a rapid increase in depressive symptoms within days to weeks after the completion of a course of ECT despite treatment with maintenance pharmacotherapy (57,70,82). For example, in a randomized, double-blind study of maintenance pharmacotherapy of psychotic depression after successful ECT (57), in which patients were assigned to maintenance therapy with nortiptyline monotherapy, nortriptyline plus lithium, or placebo, 50% of the patients relapsed within six months.

In the absence of further data, it has been my practice to leave a patient on the combination of the antidepressant/antipsychotic that they responded to for four months. After four months, if the patient has continued to remain in remission, I will begin a gradual taper of the antipsychotic medication, leaving the patient on the antidepressant. If the patient is having significant side effects (e.g., signs of tardive dyskinesia with an older antipsychotic medication or metabolic syndrome symptoms with a newer antipsychotic agent), I may start the taper earlier than four months. On the other hand, if the patient is not having any side effects, and/or is still symptomatic, I may delay the taper of the antipsychotic medication beyond four months. I usually will leave the patient on the antidepressant indefinitely, given the high rate of relapse in psychotic depression and the significant morbidity and mortality associated with relapses.

SUMMARY

In summary, psychotic depression is associated with significant morbidity and mortality. Currently, the most effective treatments include the combination of an antidepressant with an antipsychotic or ECT. Recent studies suggest that atypical antipsychotic medications may be effective (when combined with an antidepressant) for the acute treatment of psychotic depression; however, there remain many questions for future research. Those that seem of greatest

importance include the following: (*i*) the efficacy and safety of atypical antipsychotic medications for maintenance treatment, (*ii*) the most efficacious treatment for continuation and maintenance therapy after ECT, (*iii*) decision trees to delineate the second and third lines of treatment when the first treatment is ineffective (24), (*iv*) the length of time patients should be maintained on medications; (*v*) the delineation of the clinical characteristics of responders to medication treatments versus ECT treatments, and (*vi*) the role of maintenance ECT. The answers to these questions would be of significant practical utility for clinicians treating patients who suffer from psychotic depression.

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15 Recognition and Treatment of Late-Life Depression

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INTRODUCTION

As recently as 1950, adults aged 65 and greater constituted only 8% of the U.S. population (1). By the year 2050, the number of older adults will have increased by a factor of seven, and this sizeable subgroup will account for more than one in five U.S. citizens. By the same year, the number of older adults with major depressive disorder (MDD) is anticipated to exceed 2.5 million, creating a disease burden that will inflict suffering on many individuals and impose a significant demand on the health care system.

At any age, depression undermines role functioning, diminishes quality of life, destroys the capacity for pleasure, and even threatens survival. Detection and treatment of depression among the elderly is complicated by depression's variant presentations in later life, the need to consider medical factors that affect diagnosis and treatment in older adults, and the effects of age on treatment response. In this chapter, an overview of these topics will be provided. For additional background material and more extensive discussion, the reader is referred to one of the excellent recent texts devoted to this topic (2–6). These and other resources also address two important topics excluded here, the detection and treatment of bipolar disorder in the elderly (7) and a more detailed discussion of the nonmajor depressive syndromes of later life (8).

EPIDEMIOLOGIC CONSIDERATIONS

MDD affects an estimated 1% to 4% of community-dwelling elders (9,10), a lower prevalence than what is seen among younger adult cohorts. Clinicians who expect to encounter a high prevalence of MDD among the elderly are often perplexed by this lower prevalence and by the observation of lower lifetime prevalence of MDD among elderly than among younger cohorts (11–17). Among the hypotheses advanced to explain these seemingly paradoxical observations, several have found support: (*i*) there is evidence for a "cohort effect" of increasing MDD prevalence among successive generations, accounting for a misleading appearance that older age (as opposed to earlier birth) is associated with decreased MDD; (*ii*) accelerated mortality of adults with MDD may indeed reduce the prevalence of MDD among older survivors; (*iii*) the most debilitated, depressed elders may go undetected in epidemiologic studies that do not visit institutional settings where these individuals are sequestered (and where a much higher rate of MDD is observed); and (*iv*) detection of MDD among the elderly may be less efficient because of cognitive impairment, insensitivity of diagnostic criteria, or inadequacy of the instruments used in data gathering (10).

In contrast to MDD, the nonmajor depressive syndromes such as dysthymic disorder and minor depressive disorder are more highly prevalent among older adults. An estimated 15% of community-dwelling elders (18) and up to 70% of elderly longterm care facility residents (19) are affected by this spectrum of disorders. Although precise characterization of this spectrum is a work in progress (8), the shared feature of these syndromes is failure to meet MDD criteria for number, duration, or severity of depressive symptoms. It is possible that a genuine increase in nonmajor depressive syndromes accompanies the observed decrease in MDD among the elderly, but a plausible alternative hypothesis is that depressive disorders take on a subsyndromal presentation among elderly patients because they tend to endorse fewer or different symptoms than that required for the MDD diagnosis.

THE CONSEQUENCES OF UNTREATED LATE-LIFE DEPRESSION

Whether major or nonmajor, the detrimental effects of untreated depressive syndromes on older adults are very consequential (9). Late-life depression often arises in the context of comorbid chronic medical illness associated with physical and cognitive impairments. Functional impairment associated with depression may result in premature institutionalization of the elderly. The prognoses of cardiac disease and possibly of other medical illnesses are worsened by comorbid depression (20). Increased suicide, most specifically among older white males, is strongly associated with MDD (21). From a broader public health perspective, MDD alone has been estimated to account for 5.2% of all the years lived with disability (YLD), with higher rates among older women (6.1%) than among older men (3.9%) (22).

DETECTION AND DIAGNOSIS

Our current population of older adults is prone to seek help for mood symptoms in primary care settings, if at all, and the diagnosis of MDD can be neglected as patient and clinician struggle to complete the many other tasks required of a primary care encounter. Effective detection and accurate diagnosis of late-life depression require that a clinician remain aware that MDD can present in both standard and disguised versions. Clinician-related factors that impede diagnosis include inadequate skills, insufficient time in light of a busy schedule, and misattribution of depressive symptoms to adverse life events or comorbid medical conditions (23–27). Patient factors that increase the difficulty of depression detection include denial and underreporting (28,29). In addition, vegetative symptoms that more reliably indicate depression among younger adults carry less specific significance among the elderly, whose sleep, appetite, or energy may be affected adversely by comorbid medical disorders or the effects of medications. Some cognitions that would point to depression earlier in life, for example, thoughts of death or a limited hopeful anticipation of the future, occur commonly in nondepressed elders (30). A depressed mood, by contrast, may be absent in an older adult despite other significant indicators of depression. This "depression without sadness" (31,32) may be accompanied by personality change, apathy, or somatization.

Bodily concerns are heightened among the elderly, and the process referred to as "somatosensory amplification" is invoked to explain the increased

focus on bowel dysfunction, pain, limited mobility, or insomnia often seen (33). These somatic complaints can seduce a clinician into excessive focus on bodily explanations at the expense of further consideration of MDD as an underlying cause of the patient's distress. In extreme form, somatic fears that cannot be assuaged represent delusional thinking that signifies depression with psychotic features, a depressive syndrome more prevalent among older than younger adults. The delusions are not always somatic, sometimes focusing instead on fears of harm, guilt over misdeeds, or other mood-congruent concerns.

In much the same way as some patients present with bodily concerns, others focus anxiously on cognitive changes and an intense fear of developing dementia. Indeed, slowed processing and executive dysfunction are commonly seen in late-life MDD, and depressive symptoms can precede the onset of a neurodegenerative disorder, creating a differential diagnostic conundrum in some cases. The characteristic cognitive disturbances of depression, however, can be differentiated from the neuropsychologic findings that characterize dementia or the mild cognitive impairment syndromes that will progress to dementias (34). Prominent executive dysfunction in late-life depression, termed the "depression executive dysfunction syndrome," (35) is a non-dementia syndrome that has, nonetheless, significant associated neuropsychologic impairment and possibly a more brittle response to antidepressant treatment. Severe cognitive complaints, such as debilitating memory dysfunction, have been described as a "dementia syndrome of depression" and appear to be associated with an enhanced likelihood of dementia.

Truly demented older adults, of course, can also and do develop depressive symptoms. The prevalence of depressive states among demented elders is thought to be high, but MDD is less frequent than more limited depressive symptoms, and MDD can be obscured by the presence of cognitive impairment that impedes self-assessment and insightful reporting of symptoms. Among demented individuals, the presence of behavioral disruptions such as screaming, aggression, self-harm, or refusal to eat should be considered possible indicators of depression, deserving further assessment.

IMPROVING DETECTION

In clinical settings, detection of late-life depression can be facilitated by increased clinician awareness, by active inquiry that includes review of records and collection of collateral information, and by assisting the patient to recognize and identify depressive symptoms. Inquiry about suspected depression should not come to a halt upon an older adult's denial of sadness or depressed mood. Prompting the patient with everyday terms for depressed mood such as "feeling sad," "blue," "down," or "without enjoyment"; or with common terms for depressive cognitions such as "discouraged," "worthless," or "purposeless" may evoke a more insightful self-report. Observation of the patient's facial expressions and bodily gestures might clash in a revealing way with what is verbalized. A thorough biopsychosocial history with particular attention to the presence of past episodes and recent stressors, current social supports, and family history will provide further valuable diagnostic information that will also assist in the medical differential diagnosis of depression and help distinguish it from other common and phenotypically overlapping psychiatric conditions of later life including adjustment disorders; depressive symptoms associated with medication, substances, or

medical disorders; normal and pathologic bereavement; and anxiety disorders, bipolar disorders, and recurrent or new psychotic disorders.

Many clinicians find it helpful to include a brief, standardized, case-finding instrument in the assessment of depressive symptoms. The geriatric depression scale (GDS), easily administered in a few minutes, is available in the public domain in many languages and in shorter and longer versions. It is one of the most frequently used case-finding tools for identifying the presence of depression (36). While the GDS has a high sensitivity (92%) and an acceptable specificity (81%), its accuracy is limited in patients whose significant cognitive impairment interferes with self-assessment and symptom report (37,38). To facilitate depression recognition among cognitively impaired individuals, Alexopoulos et al. developed the Cornell depression scale, a 19-item scale that gathers information from both direct observation and a caregiver's report (39). Although this tool has good sensitivity and specificity (90% and 75%, respectively), its emphasis on neurovegetative depressive symptoms may result in overlooking demented patients with a masked or disguised manifestation of depression.

Other available depression-rating scales include the Beck depression inventory (BDI), the minimum data set depression rating scale (MDS) (40) used with nursing home residents, the brief assessment schedule depression scale (BASDEC) (41) used for hospitalized geriatric patients, the Center for Epidemiological Studies depression scale (CES-D) (42) that is often used in population studies, and the Montgomery Asberg depression rating scale (MADRS) (43,44) that is often used in antidepressant trials.

No standards have been set for the role of physical examination and laboratory testing in the assessment of depressed older adults, but the high rate of comorbid medical disorders in this population suggests that the use of these evaluative aids should be thoughtfully considered. A clinician's first glance will take in evidence of a depressive or anxious facial expression, signs of fatigue or sleeplessness, and indications of recent weight changes and poor self-care. The presence of physical signs such as Parkinsonian tremor, gait instability, pallor, cyanosis, or impaired respiration will help guide subsequent evaluation of affected individuals. Measurement of pulse and blood pressure can be quickly accomplished and may influence diagnostic and treatment decisions. If a thorough physical examination with laboratory testing has not been performed within the past six months (or subsequent to a severe medical event in the patient's life), it is often prudent to perform such an examination or to collaborate with a primary care colleague who will assess the patient's overall physical status. Blood and urine tests are often obtained to screen for undetected medical disorders that can produce mood symptoms. These tests can also establish a baseline in the event that a later adverse treatment response raises questions about the safety of a prescribed depression medication. A typical laboratory battery includes complete blood count, metabolic profile, thyroid function tests, and serum levels of B_{12} and folate. When clinically indicated, such additional tests as urine culture, sedimentation rate, VDRL or RPR, Lyme antibodies, antithyroid antibodies, HIV antibodies, antinuclear antibodies, or C-reactive protein may be desired. Access to neuroimaging may be limited by location or insurance, but should be considered in cases where it is appropriate to look for detectable medical sources of secondary depression such as silent ischemic brain disease, primary or secondary brain masses, or when electroconvulsive therapy (ECT) is to be considered. Although nondiagnostic and unlikely to exert decisive

effects on antidepressant choice, magnetic resonance imaging (MRI) and computed tomography (CT) changes associated with late-life depression include decreased prefrontal volumes and localized left-hemisphere infarcts that appear to be associated with depressive symptoms (45,46). These imaging findings may also have prognostic significance.

INITIATING TREATMENT

Once a diagnosis of MDD has been reached, clinician and patient can review the treatment options. Many randomized controlled trials and several meta-analyses document the effectiveness of antidepressant treatment of late-life MDD (47). A smaller number of studies show psychotherapy effective in treating MDD in older adults whose disorder is nonpsychotic, of mild to moderate severity, and not associated with severe cognitive impairment. ECT, also demonstrated effective in late-life MDD (48), is often reserved for patients who fail an initial trial of medication, so the initial treatment choice is typically between medications and psychotherapy.

The most convincing empirical psychotherapy treatment literature for MDD in older adults focuses on treatments that are time limited, focused, and structured rather than exploratory and open ended, and guided toward development of more adaptive behaviors and cognitions. Cognitive-behavioral therapy, problem-solving therapy, and interpersonal therapy have each been demonstrated effective in elderly depressed cohorts (49). Because the availability of geriatric-trained psychotherapists may be limited in many locations and because treatment of late-life depression often begins in the primary care setting where somatic treatments may be more familiar approaches, antidepressants are often the first treatment intervention. The principles guiding pharmacotherapy of the elderly will be discussed, followed by a brief overview of currently available agents.

The familiar clinical axiom for geriatric pharmacotherapy is "start low and go slow." This pearl summarizes the treatment modifications required by age-associated changes in the ways medications are handled by the body (pharmacokinetics) and in the body's response to medications (pharmacodynamics). Pharmacokinetic factors that can increase the levels or potency of medications include diminished volume of distribution, age-associated decreases in plasma albumin, and consequent elevation of the free fraction of highly protein-bound medications, diminished hepatic inactivation of drugs and their active metabolites, and reduced glomerular filtration resulting in slower drug elimination. Although several factors such as lower gastric pH, diminished mesenteric blood flow, and reduced intestinal absorption area can decrease drug absorption, typically, the overall effect of age on pharmacokinetics is to increase drugs' peak blood levels and prolong their durations of action.

The clinical importance of elevated drug levels or duration of action can be further magnified because of pharmacodynamic changes typical among older adults, which include greater sensitivity to anticholinergic adverse effects. Concurrently prescribed medications set the stage for drug-drug interactions that can further affect psychotropic drug blood levels, alter their therapeutic effects, and alleviate or exacerbate their side effects. Keeping in mind that some age-associated effects or drug-drug interactions may actually diminish the effects of a prescribed drug, an updated clinical guideline for treatment is "start low, go slow, but do not undertreat."

THE PACE OF TREATMENT INITATION AND CONTINUATION

Data from antidepressant trials of various durations suggest that older adults respond more slowly than younger adults to antidepressant treatment. It is routine, for example, to see a significant improvement in a younger adult responder after two to three weeks of treatment, but longer intervals may be required to see significant improvement in older patients. Georgotas et al. (50), for example, treated late-life MDD with phenelzine or nortriptyline and showed that most symptoms improved after the fourth week of treatment. Dew et al., reporting on a nortriptyline trial in late-life depression (51), found that a subgroup of eventual responders failed to meet recovery criteria before the tenth week of treatment. Acute antidepressant treatment response in older depressed patients should be anticipated to take 3 to 10 weeks, perhaps, and this extended duration of a drug trial is consistent with the recommendation of the expert consensus guideline (52), which endorses waiting a minimum of 2 to 3 weeks but as long as 7.5 weeks before considering an antidepressant trial adequate. In line with this suggestion, a current evidence-based recommendation is that significant improvement during the first four to six weeks of antidepressant treatment of older adults appears to identify patients who are likely to benefit from treatment continuation, while a modification of treatment approach should be considered for nonimprovers (53).

Following acute response and/or remission of depression to antidepressant treatment, a continuation phase begins. As with younger patients, lowering of the effective antidepressant dose is discouraged and monitoring of side effects and treatment adherence remain important. In contrast to the 4 to 6 months of continuation treatment recommended for younger adults, an expert consensus suggested 6 to 12 months to be appropriate for older patients (52). The goal of this treatment phase is to consolidate gains and prevent relapse, which is defined as reemergence of depressive symptoms associated with the treated episode.

CHOICE OF ANTIDEPRESSANT

A substantial evidence base supports the efficacy of antidepressant treatment of late-life depression (47). Response rates range typically between 50% and 65%, versus 25% to 30% for placebo, and remission rates vary between 30% and 40%, versus 15% for placebo (54). The majority of studies treat the younger members of the geriatric cohort, excluding many whose conditions are of interest to clinicians: the medically ill, the post-stroke elderly, the demented, the substance abusers, and those with nonmajor depressive syndromes. Ambulatory populations have been chosen in general, with relatively few studies in residential care settings.

Selective Serotonin Reuptake Inhibitors

As a result of their familiarity, ease of use, and general tolerability, selective serotonin reuptake inhibitors (SSRIs) are often the first antidepressants employed in treating late-life depression. Comparison studies do not clearly identify a superior agent among the available choices. The antidepressant efficacies of fluoxetine (Prozac, Prozac Weekly, and others), sertraline (Zoloft and others), paroxetine (Paxil, Paxil CR, Pexeva, and others), fluvoxamine (Luvox and others), citalopram (Celexa and others), and escitalopram (Lexapro) have been shown

similar to those of other antidepressants, and some evidence supports the notion of a more tolerable side effect profile than that of heterocyclic antidepressants (HCAs) (55). The SSRIs lack significant anti-adrenergic effects that might cause postural hypotension; antihistaminic effects associated with sedation and increased appetite; and with the exception of paroxetine the SSRIs lack anticholinergic effects associated with dry mouth, constipation, urinary hesitancy or retention, and erectile dysfunction. Cardiotoxicity is minimal at conventional dosing levels, reducing the risk of overdose. SSRIs, nonetheless, are all associated to some degree with the side effects of nausea, anxiety, anorexia, diarrhea, dizziness, nervousness, headache, sexual dysfunction, or insomnia. In vulnerable individuals, mania can be induced. Hyponatremia, extrapyramidal side effects such as akathisia, and insomnia or vivid dreams can complicate the course of SSRI treatment. Citalopram and sertraline are considered appropriate SSRIs for an initial trial (47,52), and this choice can be justified on the basis of the following shared desirable properties: generic availability, positive randomized controlled treatment trials in elderly depressed cohorts, minimal cytochrome P450 interactions, and an elimination half-life consistent with rational once-daily dosing. An initial citalopram dose of 10 to 20 mg/day or an initial sertraline dose of 25 to 50 mg/day can be increased if tolerated over the course of one to two months to the typical therapeutic dosing levels of 20 to 40 mg/day for citalopram and 50 to 150 mg/day for sertraline. Two additional serotonergic agents are available but infrequently used as a primary antidepressant treatment at this time: trazodone's role is more often as a hypnotic given in conjunction with another antidepressant, and nefazodone's popularity declined following the report of its association (56) with several cases of liver failure.

Serotonin-Norepinephrine Reuptake Inhibitors

Venlafaxine (Effexor and others, Effexor XR), duloxetine (Cymbalta), and desvenlafaxine (Pristiq, a newly marketed active metabolite of venlafaxine) offer alternatives that may be most appropriate after the failure of one or more SSRI trials. Serotonin-norepinephrine reuptake inhibitors (SNRIs) differ from SSRIs in that they block the presynaptic reuptake of both norepinephrine and serotonin rather than of serotonin alone. Although some data suggest the association of greater antidepressant efficacy with dual action agents in comparison with SSRIs, this claim remains to be demonstrated in the elderly. Only venlafaxine and duloxetine have already been reported effective in elderly cohorts. Venlafaxine's tendency at higher dose levels to increase blood pressure is regarded by some clinicians as a relative drawback when treating the elderly and suggests the advisability of blood pressure monitoring when venlafaxine is prescribed. Other SNRI side effects overlap with those of SSRIs, although the occurrence of discontinuation symptoms after one or two missed doses is an especial characteristic of venlafaxine, as a consequence of its short elimination half-life. In light of evidence supporting an analgesic effect of duloxetine on certain varieties of somatic pain such as those associated with diabetic polyneuropathy or fibromyalgia, this SNRI may be particularly useful for treating patients whose late-life depression is exacerbated by these additional afflictions. As with SSRIs, the geriatric dosing of SNRIs begins low but can increase as tolerated and indicated across the full range of doses used with younger adults.

Noradrenergic Antidepressants

Bupropion (Wellbutrin, Wellbutrin SR, Wellbutrin XL, and others) is the only norepinephrine-dopamine reuptake inhibitor (NDRI) available in the United States at present. Bupropion is contraindicated in patients with a seizure disorder, a current or prior diagnosis of bulimia or anxorexia nervosa, or patients undergoing abrupt discontinuation of alcohol or sedatives including benzodiazepines. An elevated risk for seizures should be discussed with patients without bupropion contraindications but who nonetheless are at increased seizure risk, for example patients who are taking other seizure-threshold lowering medications. The slow and extended-release preparations (bupropion SR and bupropion XL) are associated with less increased seizure risk. Bupropion has been shown effective in the elderly, and its use is associated with minimal sedation, weight gain, or sexual dysfunction. Bupropion's mechanism of action does not suggest an antianxiety effect, yet a comparison of bupropion SR with paroxetine in elderly depressed subjects showed no increased rate of treatment-emergent anxiety with bupropion (57). Treatment of psychotic depression with bupropion is not recommended. In the elderly, bupropion treatment can be initiated at 75 mg/day of the immediate-release form or 100 mg/day of the slow-release form. To decrease the seizure risk, individual doses do not exceed 200 mg except with the XL form, which can be dosed up to 300 mg at a single administration. Daily dosing of up to 450 mg/day has been tolerable and effective in late-life depression studies, but doses between 200 and 300 mg/day often suffice. Common side effects include headache, somnolence, insomnia, agitation, dizziness, diarrhea, dry mouth, or nausea.

Mirtazapine (Remeron and others), a noradrenergic agent characterized by very different side effects and mechanism of action, antagonizes presynaptic noradrenergic α-2 autoreceptors and heteroreceptors and H_1, $5HT_2$, and $5HT_3$ receptors. Its antidepressant effect is often accompanied by sedation, appetite enhancement, but little, if any, nausea. This combination of effects is often desirable in the treatment of anxious, insomniac, anorexic elderly depressives. Mirtazapine has been found effective and tolerable in the elderly (58–60), though sedation (perhaps especially at lower doses) and weight gain can undermine adherence.

Heterocyclic Antidepressants and Monoamine Oxidase Inhibitors

Use of the HCAs and monoamine oxidase inhibitors (MAOIs) is beset with the potential for more severe adverse effects in elderly patients, yet these medications remain a consideration for patients who fail to respond to newer agents. HCA use has been associated with sedation, fatigue, toxicity in overdose, cardiovascular risks, and anticholinergic effects such as blurred vision, dry mouth, severe constipation, or urinary retention (61). These side effects are less severe with the secondary amines such as nortriptyline and desipramine. Nortriptyline, in particular, has been well studied with elderly cohorts. A meaningful window of therapeutic serum level ranges guides dosing and increases the likelihood of avoiding toxic drug dosage levels. When its use is optimized by monitoring serum levels, nortriptyline is as well tolerated and as effective as serotonin reuptake inhibitors, although its particular adverse effect profile can be problematic for

older adults (62). In the elderly, typical dosing begins at 10 to 30 mg/day, with a serum level target between 50 and 150 ng/mL, usually achieved at doses between 40 and 100 mg/day. Dosing of desipramine, a secondary-amine HCA alternative, can be initiated at 10 to 25 mg/day and gradually increased to the 150 to 200 mg/day range in some patients. A pretreatment electrocardiogram is made necessary by heterocyclics' quinidine-like effects on cardiac conduction, and these effects can add an unacceptable level of risk to the treatment of patients with bundle branch disease. Orthostatic hypotension, which can increase the risk of a fall, is less severe with nortriptyline than with other heterocyclics (63). In general, careful monitoring of side effects and use of the lowest effective dose are important treatment principles with the heterocyclics.

Among the five currently available MAOIs, phenelzine (Nardil and others) and moclobemide (not available in the United States) are two that have been shown effective in treating late-life depression. The MAOIs' potential for toxic drug-drug or drug-food interactions limits their use despite comparable antidepressant effectiveness. These antidepressants work by inhibiting the monoamine oxidase (MAO) enzyme that breaks down catecholamines and indoleamines in presynaptic neurons and in the synapses, but MAO located in the intestines is also inhibited, rendering the body vulnerable to ingested "false neurotransmitter" molecules in food. Although the "MAOI diet" is well understood, adherence may be problematic, particularly in patients with some degree of cognitive impairment if they are continuing to prepare their own meals. In addition, medications that increase the presence of genuine neurotransmitters in the CNS, such as other antidepressants, have the potential to interact adversely with MAOIs (although some combination treatments have been used, with special precautions, in treatment-resistant younger adults). Typical MAOI side effects include increased appetite and weight gain, induction of mania or hypomania, orthostatic hypotension, sexual dysfunction including inhibition of orgasm, swelling of the ankles or feet, increased sweating, skin rash, constipation, drowsiness, dry mouth, insomnia, nightmares, or fatigue. Periodic monitoring of hepatic transaminases is suggested. Switching between MAOIs is just as dangerous as switching between MAOIs and other types of antidepressants, and the timing of a switch requires planning particularly with medications such as fluoxetine, which, because of its long elimination half-life, should be allowed to wash out five weeks before initiating an MAOI trial. A new transdermal preparation of the selective MAOI, selegiline (Emsam transdermal), offers an alternate route for antidepressant administration but has not yet been specifically tested in elderly cohorts.

Stimulants

As an alternative to standard antidepressants, some clinicians have treated late-life depressive states with stimulants such as methylphenidate. A minimal amount of evidence supports this approach, although a very brief controlled trial among medically ill, depressed, geriatric patients is often cited (64) and a number of case series have been published as well. Because of their rapid effects, stimulants are sometimes suggested for use in medical settings where a quick response is desired. Apathetic patients and those intolerant to standard antidepressants may be appropriate for such a trial, often starting at 2.5 to 5.0 mg

each morning and increasing to as high as 20 to 30 mg/day in divided doses with careful monitoring of cardiovascular response, sleep, activity, and appetite.

ADDITIONAL SIDE-EFFECT CONSIDERATIONS

For clinicians unfamiliar with the treatment of older adults, the management of routine side effects requires a fresh look. Side effects such as weight gain, daytime sedation, or sexual dysfunction, very important to younger patients, may be tolerated more acceptingly by older adults. Falls, hyponatremia, and increased bleeding, on the other hand, may be life threatening in the older patients and demand clinician awareness.

Fall risk, which may not even routinely be discussed when prescribing an antidepressant to a younger patient, increases with age (65) and with the use of psychotropic drugs (66). Falls represent damaging and debilitating crises into the lives of older adults. Not only the heterocyclics but also serotonergic antidepressants increase fall risk (67,68). In light of evidence for greater fracture risk among the depressed elderly as a result of suspected decreases in bone mass density associated both with depression and with serotonergic antidepressant treatment (69,70), assessment for treatment of late-life depression should consider the spectrum of fall risks, including gait instability, visual impairment, vertigo or lightheadedness, confusion, use of sedating medications, substance use, or a positive history for prior falls.

Hyponatremia, a known antidepressant side effect that occurs more frequently with serotonergic antidepressants and with greater incidence among older patients (71,72), can result in lethargy, confusion, convulsion, coma, delirium, and even death in severe cases. The greatest risk for this treatment complication occurs in older patients, females, patients using concomitant diuretics, those with low body weight, and those with lower-baseline sodium level. SSRI-associated hyponatremia often develops early in treatment. It should resolve within two weeks of antidepressant discontinuation. An SSRI rechallenge may result in hyponatremia as well, and should therefore be monitored (73). Abrupt falls in sodium levels are more likely to produce distressing symptoms. Baseline electrolyte measurement will detect hyponatremia, and patients at greatest risk may warrant repeat measurement one month after treatment initiation.

Increased risk for bleeding with serotonergic antidepressants has been explained as due to effects on platelet aggregation and vascular tone (74). Increased risk for upper gastrointestinal bleeding with SSRIs versus other antidepressants has been reported (75,76). The greatest risk is among the oldest patients and among previous gastrointestinal bleeders (77). A history of bleeding suggests caution and the presence of concurrent risk factors for gastrointestinal bleeding, for example, the use of nonsteroidal anti-inflammatory drugs or alcohol abuse should be considered when prescribing an SSRI.

SPECIAL TREATMENT POPULATIONS

Among older adults with MDD, questions are often raised regarding the special needs of common patient subgroups: long-term care facility residents, the depressed, medically ill patient, the delusional, depressed patient, the demented, depressed patient, and the patient with treatment resistance. Each of these topics will be briefly addressed.

The 5% of older adults who reside in *long-term care facilities* are thought to represent a population among which minor and major depressions are common but treatment is underutilized. A recent study, for example, reported that only 55% of the depressed LTCF residents assessed were receiving antidepressants and 32% of these were treated with subtherapeutic dosing (78). Because depression in LTCFs can be debilitating and persistent, clinicians working in LTCF settings should be alert to the possibility of depression and can increase case finding by educating caregiving staff about depression and about the simple tools available for its detection. No current standard suggests a different approach to treatment of LTCF residents than that of other older adults, but case finding requires special attention.

Depression comorbid with medical disorders is more frequent among older than among younger adults. Arthritis, cancer, diabetes, and vascular disease are among the many conditions that increase with age and can profoundly affect mood. Vascular disease has been of special interest with respect to late-life depression because cerebrovascular disease has been linked with a specific variety of depression termed *vascular depression*. In this syndrome (35), which bears some similarities to the syndromes of *subcortical ischemic depression* and *depression with executive dysfunction*, cognitive impairment is present but is often of a variety and severity that fails to merit the diagnosis of dementia. In collaboration with the patient's PCP, CVA risk factors can be addressed. Problem-solving therapy and antidepressant treatments appear helpful, though response may take longer and persist more briefly.

The key questions for clinicians to ask in case of depressed, medically ill patients are (*i*) to what extent depressive symptoms are manifestations of a medical illness that requires specific nonpsychiatric treatment in addition to psychiatric care, (*ii*) how depression might affect the course of the medical illness(es), and (*iii*) how the presence of the medical illness(es) will interact with the proposed antidepressant or ECT treatment. For example, will side effects be exacerbated? Will treatments for the medical and psychiatric symptoms interact adversely with each other? Will the presence of depression affect adherence to a medical treatment plan? These questions, and the reciprocal relationship that often exists between medical and depressive symptoms, have been reviewed extensively elsewhere (4–6,79) and recently by Harnett and Pies (20).

Delusional depression, relatively more common in older than in younger adults (80), has been studied to only a limited degree in older cohorts. The accepted treatment approach, which needs confirmatory studies in the elderly, has been to combine an antidepressant with an antipsychotic agent (152). Whether the increased mortality associated with antipsychotic medications in psychotic, demented older adults is also present in psychotic, non-demented older patients is not known. In the absence of more detailed evidence, however, clinicians should educate patients (or their health care representatives when that is more appropriate) about current concerns regarding antipsychotics' adverse effects. In any case, the antipsychotic should be prescribed at the lowest effective dose and for the briefest necessary interval. ECT is a highly effective nonpharmacologic treatment that can be offered as an alternative to pharmacotherapy (48).

Dementia with depression is relatively rare among younger adults, but the higher frequency of cognitive impairment in the elderly and the very high frequency of depressive symptoms among the cognitively impaired make this syndrome important among the elderly. Up to one half of demented patients

develop significant depression, but symptoms may go unnoticed among those unable to describe their distress because of cognitive or language difficulties. Furthermore, key symptoms such as apathy, passivity, decreased initiative, and poor concentration are common to both dementia and depression and may obscure their comorbid presence. Placebo-controlled trials have shown pharmacotherapy to relieve depressive symptoms in groups of depressed, demented subjects (81). Sertraline and citalopram are among the medications that have produced positive results. Some experts suggest use of lower doses (82) or concurrent behavioral intervention (52).

Treatment-resistant depression, defined as failure to respond to at least two adequate antidepressant trials, presents a difficult challenge in the treatment of late-life MDD. Initially, a diagnostic review should consider whether prior treatment has been Adequate, whether Behavioral factors such as relationship or environmental stress have been addressed, whether Compliance (or adherence) has been adequate to deem a previous trial failed, and whether additional Diagnoses such as psychosis, substance abuse, medical illness, or personality disorders should be considered. This A-B-C-D mnemonic filters out individuals whose distress requires more than additional antidepressant treatment. The remainder of individuals can proceed to a trial of switching or augmentation/co-prescribing (47).

Because switching may require a cross taper and/or a "wash out" period, it is a slower approach that is more suitable to work with outpatients and less severe depression. STAR*D results suggest that it is rational to switch either within or out of the initial antidepressant class, though some clinicians are accustomed to choosing a second antidepressant with a different mechanism of action. The choice of antidepressant should take into account the patient's prior treatment experiences, medical risk factors, specific side effect preferences, formulary availability, and cost. No specific antidepressant has been determined to be more effective than others in this switch process. The first two antidepressants often come from newer drug classes, but subsequent trials may draw on older classes such as the heterocyclics or MAOIs or may introduce a nonpharmacologic strategy such as psychotherapy or ECT.

In those for whom speed of response is critical or who feel invested in a partially effective current antidepressant, an *augmentation/co-prescribing* strategy is often pursued. Evidence has not shown this approach more safe or effective, and it results in increased cost and complexity. No medication is currently FDA indicated for augmentation of depression treatment, with the exception of aripiprazole, an atypical antipsychotic recently indicated for this purpose. Augmentation using medications outside of their FDA-indicated roles is permissible when clinically justified, provided that patients are appropriately informed regarding such a nonindicated treatment approach and the adverse effects that may accompany it. Such off-label approaches and polypharmacy should be reserved, however, for patients who have already received and failed appropriate standard treatments.

Augmenters are defined as agents not considered to have independent antidepressant properties. Augmenters used in the elderly are the same as those used in younger adults, though their use in older cohorts is less evidence based. Lithium carbonate (Li_2CO_3) augmentation, typically at blood levels between 0.4 and 0.8 mmol/L, has been efficacious in older adults (4,83) but associated with significant cognitive and somatic adverse effects. Triiodothyronine (T_3), often

used with benefit in younger adults at doses between 5 and 50 mcg/day, has not been specifically studied in older cohorts (84). Even at these relatively low doses of T_3, side effects such as anxiety, tremor, or insomnia may complicate the treatment of late-life MDD. Methylphenidate (5–20 mg/day) and other stimulants have been reported beneficial as antidepressant augmenters or as treatment accelerators in the elderly (85, 86). Modafinil, a stimulant-like medication, has been associated with mixed augmentation effectiveness in younger adults, and the evidence base for its use in this way in depressed geriatric patients is slim (87).

Co-prescribing is the term that describes addition to an antidepressant of an additional agent possessed of independent antidepressant properties. No antidepressant is specifically labeled by the FDA as indicated for this purpose. Bupropion can be added to a partially effective serotonergic agent in the treatment of medically frail elderly subjects (88). Low-dose nortriptyline, for example, 10 to 25 mg at bedtime, can provide a more sedating co-prescribed antidepressant that requires consideration of potential cytochrome 2D6 interactions such as those likely to occur with concurrent paroxetine or fluoxetine, each an inhibitor of the 2D6 enzyme involved in nortriptyline's metabolism (89). Mirtazapine, beneficially co-prescribed in younger depressed adults, is often added to a serotonergic antidepressant to assist depressed older adults' sleep. Doses range from 7.5 mg to 45 mg at the hour of sleep. The atypical antipsychotics, despite FDA warnings regarding their mortality-increasing effects on psychotic demented patients, are frequently co-prescribed with antidepressants even for nonpsychotic elderly patients. This practice is supported in the elderly by two open-label trials. In one, aripiprazole up to 15 mg/day increased the benefit of antidepressant treatment in an elderly cohort, though adverse effects and dropouts were frequent (90). Risperidone, the other antipsychotic studied in this way, produced more remissions than placebo when co-prescribed at doses of 0.25 to 1 mg/day with citalopram 20 to 40 mg/day to a cohort of treatment-resistant, depressed older adults (91). A final augmenting agent, testosterone, used in hypogonadal depressed treatment-resistant men, has shown promise (92), but its use must be avoided in men with medical contraindications such as prostate cancer or hepatic disease.

Given the limitations of our current medications, a proportion of individuals will be unhelped by even multiple trials of pharmacotherapeutic agents. For some, the addition of psychotherapy may help by strengthening defenses or readjusting expectations and other cognitions. In others, the nonpharmacologic approaches that can be considered include ECT or a still-experimental treatment, transcranial magnetic stimulation (TCMS). ECT and TCMS have recently been reviewed in detail elsewhere (48).

MAINTENANCE TREATMENT IN LATE-LIFE MAJOR DEPRESSIVE DISORDER

After the 6- to 12-month continuation phase of treatment recommended in late-life MDD, some patients should be advised to enter a maintenance phase of treatment. Consensus at this time supports a lower threshold for maintenance treatment in elderly patients, particularly those with more prior episodes of depression, more severe past episodes, concomitant anxiety symptoms (52), or delayed response in the first episode (93). Maintenance treatment of one year or more is suggested following a severe first or a second episode and for three or more years following a third or subsequent episode (52).

CONCLUSION

As our older adult population increases in number and late-life MDD becomes more prevalent, it will be important for primary care clinicians and specialists to increase their expertise in treating this debilitating condition. Further studies are needed to determine the optimal treatment practices, but enough is already known to encourage active case-finding efforts and treatment recommendations. Armed with a greater awareness of depression's varied presentations in later life, an understanding of the interactions between depression and medical illnesses, a knowledge of the full range of available treatment approaches, and evidence-based information about the potential benefits of treatment, clinicians can ease the suffering and improve the quality of life for many depressed older adults in need of informed and optimistic treatment.

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16 Fibromyalgia: A Prototype Illness of Pain and Depression Comorbidity

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This chapter collects and synthesizes up-to-date information about the complex etiologic theories and treatment regimens associated with fibromyalgia (FM) and its association with depressive syndromes. There are many overlapping pain and depression comorbidities, and we have specifically chosen to review depression and FM for a few reasons. First, FM has been a controversial illness with several proposed etiologies. Second, FM may be more of a neuropathic pain condition with organic and functional etiologic overlap with depression pathology. Third, in the last year we have gathered three new FDA approvals for treating this pain disorder. Fourth, many of the neuropathic and nociceptive treatment options that we discuss can easily be applied to other pain conditions associated with depression.

We first review current epidemiologic and etiologic theories regarding pain disorders and depression. Again, we will be using FM as a prototype overlap of pain and depression, but other interactions between pain and depression certainly occur, and the same neurologic principles apply. A formal literature review is next presented to allow the reader to understand the evidence base that supports treatment of this disorder. A thorough MEDLINE search was utilized to collect many papers dedicated to this topic spanning 1970 to 2008. The relevant papers were divided on the basis of intervention used for the treatment of FM (pharmacologic vs. nonpharmacologic). Below, we will first review current epidemiologic and etiologic theories regarding pain disorders and depression. Then, we will comment on the treatment of FM and its comorbidity with depression in the context of pharmacodynamics and other management strategies.

Outside FM and depression, there are similar pathways and interactions between other chronic painful conditions and depression. In a review, Leo et al. suggest that headaches, temporal mandibular joint (TMJ) syndrome, irritable bowel syndrome (IBS), post-stroke central pain, multiple sclerosis, Parkinson's disease, osteoarthritis, and rheumatoid arthritis are all diseases and syndromes that often present with pain in psychiatric practice (1). Conversely there seems to be an inordinate amount of patients with depression, anxiety, substance misuse, and personality disorder that present with painful conditions as well. Altered pain perception and tolerability in controlled laboratory settings has also been demonstrated in patients with schizophrenia, bipolar disorder, anxiety, depression, and borderline personality disorder (2–5). Chronic pain may be a risk factor for suicidal thinking and attempts. Pain may be a risk factor for suicidal behavior, independent of baseline presence of mental illness or not.

Abdominal pain and musculoskeletal pain have been associated with increased suicidality (6,7). Finally, pain is a negative predictor of response to treatment in depression and also may predispose to easier and more frequent relapse back into depressive episodes after remission is obtained (8,9). These complex interactions between pain and mental disorder may affect symptom burden, disability, treatment outcome, and even morbidity and mortality.

Specifically, headaches and depression share a great deal of comorbidity, with approximately 50% of patients with major depressive disorder (MDD) also suffering from chronic headaches and roughly vice versa (10). Also, duloxetine has found to be helpful as a preventative in the treatment of chronic headache with comorbid depression, independent of its antidepressant effects, similar to findings in FM (10). Similarly, there is evidence that central sensitization may at least contribute to the pathophysiology of chronic headache and IBS (11,12). Finally, there is increased disability and decreased quality of life in comorbid arthritis and depression, similar to comorbid FM and depression (13–15). For all these reasons, the prototype of FM and depression can shed light on possible common pathophysiologic mechanisms and quality of life issues involving pain disorders generally in the context of depression.

INTRODUCTION

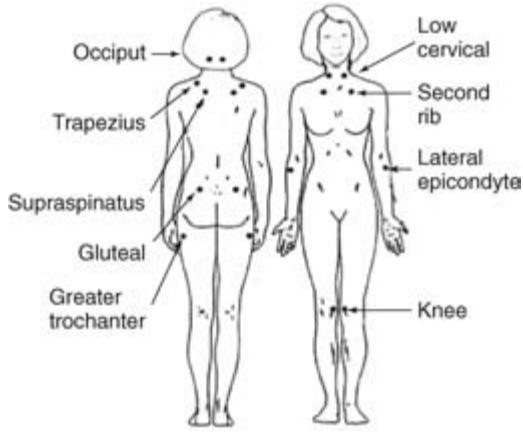
FM is a complex disorder with many associated symptoms. It affects 2% of the U.S. population, approximately 3.7 million people in the United States (16). The establishment of FM as a diagnosis has been an evolving process with the absence of definitive criteria until 1990. In 1990, the American College of Rheumatology published its research-based criteria, which is now the standard when diagnosing FM (Table 1) (17).

FM occurs seven times more frequently in women than in men, and it occurs most frequently in women of childbearing age. Prevalence is 3.5% in women as compared with 0.5% in men (18). In outpatient rheumatology settings, 10% to 20% of patients seeking care have FM, while in outpatient, non-rheumatology settings, the prevalence is lower at 2.1% to 5.7%. In women between the ages of 60 and 79 years, the prevalence tends to be lower than expected at 7% (18). Ninety percent of FM patients will have jaw and facial tenderness, especially pain on opening and closing their mouth, and the jaws having a "tight" sensation. These symptoms are similar to those seen with TMJ disease. In patients with FM, 50% suffer from sensitivities to various elements in the environment such as odors, noise, and bright lights. Some may have sensitivities to medications and various foods.

The treatment of FM is also important because of the deleterious impact it has on the economic condition and productivity of society. In one study, 26% of FM patients surveyed received some form of disability payment. The average cost of treating an FM patient was $2274 per year. Despite a variety of treatments employed, patients tended to show no clear sustained response over a seven-year follow-up period. Over $20 billion per year are spent on FM patients because physicians are unable to provide them with clear single therapies that work. Multimodal treatment is the norm. Despite this huge socioeconomic burden and frustrating attempts by clinicians to treat the pain, the quality of life for a person with FM remains poor (19).

TABLE 1 Criteria of Fibromyalgia

1. History of widespread pain for at least 3 months. Pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or lower back) must be present. In this definition, buttock and shoulder pain is considered as pain for each involved site. "Low back" is considered lower segmental pain.
2. Pain in 11 of 18 tender points on digital palpation.



Occiput: Bilateral, at the suboccipital muscle insertions.
Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5–C7.
Trapezius: bilateral, at the midpoint of the upper border.
Supraspinatus: bilateral, at origins, above the scapula spine near the medial border.
Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces.
Lateral epicondyle: bilateral, 2 cm distal to the epicondyles.
Gluteal: bilateral, in upper outer quadrants of buttocks in anterior fold of muscle.
Greater trochanter: bilateral, posterior to the trochanteric prominence.
Knee: bilateral, at the medial fat pad proximal to the joint line.

Digital palpation should be performed with an approximate force of 4 kg.
For a tender point to be considered "positive" the subject must state that the palpation was painful. "Tender" is not to be considered "painful."

Given the impact of this illness and the overlap in care between primary care, rheumatology, neurology, and psychiatry, the authors have compiled a comprehensive review of treatment options available for the treatment of FM. As the authors are practicing psychiatrists, this chapter is written from a psychiatric point of view. The chapter also utilizes an evidence-based approach where the reader will not only receive a comprehensive review of FM treatments but also gain some understanding in regard to the most well-studied treatments versus more anecdotal options. We will suggest some clinical options for the psychopharmacologist to consider if FM patients are encountered in psychiatric practice. We will discuss the etiology, clinical presentation, nonpharmacologic, and pharmacologic treatment options for FM throughout the paper.

ETIOLOGY

FM is a controversial syndrome due to the presence of a large range of symptoms affecting multiple systems in the body and the difficulty in characterizing it into a specific systemic category. It is characterized by persistent widespread pain, abnormal pain sensitivity, and additional symptoms such as fatigue, executive dysfunction, sleep disturbance, and mood symptoms. Although the exact etiology and pathogenesis of FM are still unknown, it has been suggested that stress or psychologic factors may play a key role in the syndrome for certain individuals, but having a mental illness is not a given if one also suffers from FM.

From 1904 to 1976, FM was known as fibrositis, an inflammatory disease, then the term "fibromyalgia" was coined because of the predominant pain symptoms in the absence of laboratory inflammatory findings seen in patients suffering from this illness (20). It was often noted that FM was associated with depression, stress, and anxiety as well. This has often been investigated, and it is often felt that these psychiatric comorbid disorders are often more a result of FM disability than the cause of FM (21–23).

Multiple etiologic theories have been proposed to explain the pathophysiology of FM. Studies suggested that the symptom of pain was present because of damage to various soft tissue organs of the body such as skeletal muscles, ligaments, and tendons, but this was ultimately disproven by the absence of any damage noted in biopsies (24).

There is a strong familial component for FM indicating but not proving a genetic basis or heritability (25–27). Key findings include familial aggregation, which is well established in FM, with extensive research focused on polymorphisms and genes related to neurotransmitters involved in CNS pain transmission processing. Furthermore, serotonergic and dopaminergic markers, as well as polymorphisms in the genes encoding cathechol-*O*-methyltransferase (COMT) and the NK_1 receptor, are among the candidates studied, and a number of significant associations have been reported. Other findings include that human leukocyte antigen (HLA) prevalence of DR4 in FM patients is 64% versus 30% in normal comparison subjects. Buskila and colleagues reported a significant decrease in the frequency of the seven repeat allele in exon 3 of the D4 receptor gene, and FM patients also demonstrated an association between this polymorphism and the low novelty–seeking personality trait (28). These findings are interesting since altered dopamine D_2 function has been demonstrated in FM patients (29) and recent evidence has demonstrated the efficacy of the dopamine-3 agonist, pramipexole, in patients with FM (30). Altogether, recent evidence suggests a role for polymorphisms of genes in the dopaminergic and catecholaminergic systems in the pathogenesis of FM.

Similar to findings in some depression studies, there is increased frequency of the "ss" allele of the serotonin transporter (SERT) gene promoter (5HTLLPR) variant and the $5HT_{2A}$ gene "TT" and "TC" T102C silent gene polymorphisms in FM (31,32). The results of one study confirmed the association between FM and the SERT promoter region polymorphism and two ethnic groups in Israel, Jews and Bedouins (33). A significant association between the 5HTTLPR polymorphism and anxiety-related personality traits was found as well. The $5HT_{2A}$ study showed a decrease in the TT as well as an increase in both TC and CC genotypes in FM patients compared with controls (32). However the increase in allele C102 frequency fell short of significance. Correlation of genotypes to clinical parameters revealed no influences on age of onset, duration

of disease, or psychopathologic syndromes, measured with the Beck Depression inventory (BDI) and the symptom checklist SCL-90-R. In contrast, pain score was significantly higher for patients with the TT genotype. It was suggested that the C102 allele might be involved in the complex circuitry of nociception. It was concluded that the T102C polymorphism is not directly involved in the etiology of FM, but might be in linkage disequilibrium with a true functional variant, which has yet to be identified (32).

For the COMT gene, it may alter dopamine and norepinephrine (NE) processing, the LL and LH polymorphisms are found more frequently among FM patients than controls, and there is a concomitant decrease in the percentage of HH variants compared with controls. This may be of some significance in the pathologic mechanism of FM. Also, Zubieta and colleagues found that individuals homozygous for the Met158 allele of the COMT polymorphism showed diminished regional μ-opioid system responses to pain compared with heterozygotes (33). These effects were accompanied by higher sensory and affective ratings of pain and a more negative internal affective state. It was concluded that the COMT Val158Met polymorphism influences the human experience of pain and may underlie interindividual differences in the adaptation and responses to pain and other stressful stimuli (33).

Abnormalities in the serotonin (SR) and NE pathways have been suspected as a possible etiology for FM as both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitor (SSRI) as well as selective norepinephrine reuptake inhibitor (SNRI) antidepressants are sometimes useful in the treatment of FM, but the exact relationship and the role of catecholamines in the etiology of FM remains unclear. Both the relative unavailability of SR and NE have been identified as key components in affective disorders such as depression and anxiety (34). In the brain, blockade of the SR and NE transporter results in an increase of available monoamines and also in a cascade of molecular events to help relieve depression and anxiety, while pain relief in FM may come from similar actions of SR and NE in the spinal cord and possibly the brain as well. These ideas are discussed in detail later. Likely, when functioning in an optimal manner, these descending monoamine pathways stimulate GABA interneurons, which then inhibit ascending pain signals from reaching the thalamus and sensory cortex. It is possible that the abnormalities, or underfunctioning in these pathways prevent the usual dampening of afferent pain signals causing an increase in perception of pain.

The increased concentration of a pain modulator, substance P, may suggest an increased peripheral sensitivity to pain for patients with FM, but this was disproven by the lack of correlation of the level of substance P compared with muscle tenderness present in the patients (35). The receptor for substance P is named NK_1. Antagonists of the NK_1 receptor have shown promising results in the treatment of such diverse conditions as depression, anxiety, and IBS; however, treating FM with these experimental compounds has met with little success (25).

Some other neuroendocrine abnormalities have been identified in FM patients (36,37), such as impairment in activation of the hypothalamic-pituitary-adrenal (HPA) axis and low 24-hour urinary free cortisol, but normal peak and elevated trough plasma cortisol levels, compared with normal subjects. There are suggestions that HPA dysfunction may be a mechanism of pathogenesis for FM's physiologic mechanisms including increase of selective

cytokines as well as cortisone levels (38). Furthermore, there is decreased resiliency of the HPA axis to return to baseline after an adrenocorticotropic hormone (ACTH) challenge, resulting in increased basal level of cortisol in FM patients (39). This suggests an overall dysfunction at the HPA axis in patients with FM. An autoimmune process was suggested to be a probable etiology of FM due to the presence of cytokines such as Interleukin-2 (IL-2) in patients with FM (40). It has not been distinguished whether the presence of this cytokine is a result or cause of FM, leaving this theory in question. Also inadequate sleep, commonly found in FM patients, can result in increased cortisol and IGF-1 factor being elevated, which can result in poor muscle tissue damage healing and interfere with sensory transmission (41). The significance of these findings in terms of the etiology of FM is still unknown.

Some other findings such as abnormalities in sleep patterns in patients with FM such as abnormal amounts of alpha wakefulness activity and decreased delta sleep on the electroencephalogram (EEG) (42) and a response to aerobic exercise programs leading to an improvement in sleep abnormalities (43) suggests alteration sleep patterns as possible etiology for FM.

Finally, one of the leading theories behind increased pain sensation, lowered pain thresholds, and clinically noted trigger points is that of central sensitization (44). This theory suggests that a remodeling or rewiring of pain and other sensory fibers occurs leading to increased pain sensation and disability. Phantom limb or reflex sympathetic dystrophy (RSD) is a prototype condition for this theory where nerves are clearly injured and even in the absence of the limb, that is, after amputation, a great amount of neuropathic pain is felt clinically by the patient. Similar RSD is seen after physical trauma, that is, crushing injuries of the extremities when the trauma, inflammation, and functional disability ultimately subsides and resolves, but immense pain continues. No one would suggest to a physical-trauma patient that the pain he or she is experiencing is all functional or psychologic after such a clear physical trauma, yet evidence on examination would show no clear physical inflammation to drive nociception. Cleary neuropathic pain occurs in these patients. It is possible that in FM this same type of RSD symptoms occur where pain signals are firing at the level of the spinal cord segment, the thalamus, or the sensory cortex even in the absence of inflammation or trauma. Medications like pregabalin and duloxetine that reduce bona fide neuropathic pain, that is, diabetic neuropathy, also lower FM pain. Duloxetine, as noted above, increases spinal SR and NE as its mechanism of pain dampening. Pregabalin is different in that it dampens calcium channel activity in pain fibers.

The mechanism of central sensitization likely occurs as follows: Initially a physical trauma occurs and inflammation results causing usual nociceptive pain. However, during this event many pain fibers are depolarized. Next, voltage-gated sodium channels open allowing further pain fiber depolarization, then calcium voltage-gated channels open further and allow more neuronal depolarization and the calcium influx allows neuronal vesicular transport to occur. The net result of this is that marked amounts of glutamate are dumped into pain fiber synapses. Glutamate is excitatory and allows even more firing of pain fibers. Glutamate is involved in learning processes and may help "glue" or solidify synapses together elsewhere in the CNS, and it is possible that the net effect of glutamate influx into the "pain" synapse allows neuropathic pain pathways to become, more or less, autonomous and able to

fire more repeatedly, fire in response to less noxious stimuli, that is, trigger/tender points. This way the pain pathways are sensitized to respond to light touch or pressure as though they were being hit by a hammer. There are now likely increased receptive pain fields, increased recruitment of pain fibers as a result of the cascade so the whole system is "ramped up" or sensitized toward firing or receiving pain signals. Medications useful in treating neuropathic pain are often epilepsy medications that decrease cortical neuronal firing to prevent seizures. These decrease recruitment and dampen neuronal firing. Sodium channel blockers like carbamazepine and calcium channel blockers like pregabalin likely dampen excessive neuronal firing in the periphery, at the level of the spinal cord segments and even possibly in the thalamus and sensory cortex as well. Their ability to diminish the cascade of sodium influx, calcium influx, and glutamate release is felt to dampen the firing of patients' pain circuitry as well.

Because of the inability of the above purely biologic theories to explain the exact pathophysiology of FM, a biopsychosocial etiology is the most practical model for the understanding of FM. Increased incidence in relatives of affected patients has been noted, which implies that inheritance may be a variable (45). Precipitating factors, such as trauma, infection, stress, or sleep deprivation may help precipitate some of the biologic changes mentioned above, leading to the onset of FM syndrome.

CLINICAL PRESENTATION AND DIAGNOSIS OF FIBROMYALGIA

The diagnostic feature of FM is the prevalence of widespread bilateral pain (Table 1). Pain is considered widespread when all of the following are present: pain in both sides of the body and/or pain above and below the waist. In addition, axial skeletal pain (cervical spine, anterior chest, thoracic spine, or low back pain) must be present.

Pain should be reproducible in 11 of 18 tender point sites upon digital palpation. The 18 tender point sites are as follows:

1. At the occiput or at the suboccipital muscle insertions.
2. Low cervical or at the anterior aspects of the intertransverse spaces at C5–C7.
3. Trapezius or at the midpoint of the upper border.
4. Supraspinatus or at origins, above the scapula spine near the medial border.
5. Second rib or upper lateral to the second costochondral junction.
6. Lateral epicondyle or at 2 cm distal to the epicondyles.
7. Gluteal or in upper outer quadrants of buttocks in anterior fold of muscle.
8. Greater trochanter or posterior to the trochanteric prominence.
9. Knee or at the medial fat pad proximal to the joint line.

Digital palpation cannot be light and must be performed with an approximate force of 4 kg. A moderate amount of pressure must be applied by the clinician to fully elicit a painful tender point response. A tender point has to be painful at palpation, not just "tender" or uncomfortable (17).

The following symptoms are often reported in descending order of occurrence; muscular pain 100%, fatigue 96%, insomnia 86%, joint pain 72%, headaches 60%, restless legs 56%, numbness and tingling 52%, impaired memory 46%, leg cramps 42%, impaired concentration 41%, nervousness 32%,

and major depression 20% (17). These "other" FM symptoms are often overlooked but clearly add to patient morbidity.

As seen from the data above, muscle pain remains the cardinal feature of FM with fatigue and insomnia following it. Although depressive symptoms are felt to be common, the presence of a major depressive episode is prevalent in only 20% of FM patients (26,34). There is a significant overlap between the symptomatology of FM, depression, dysthymia, and generalized anxiety. The implication in regards to etiology and potential treatment is that perhaps common neural pathways may both mediate and treat psychiatric and FM syndromes.

Most of the studies conducted on the correlation of comorbidity with FM suggest that the prevalence of depression and anxiety disorders is significant in patients with FM. In one study, 73 subjects with FM were found to have a high lifetime and current prevalence of major depression and panic disorder. The most common disorders were major depression [lifetime (L) = 68%, current (C) = 22%], dysthymia (only C = 10%), panic disorder (L = 16%, C = 7%), and simple phobia (L = 16%, C = 12%). Functional impairment on all measures of the social functioning 36 scale was severe (e.g., physical functioning = 45.5 and role limitations due to physical problems = 20.0) (46). A study of 115 patients, which looked at the functionality of FM patients with respect to coping mechanisms for pain, divided the patients into three groups; the "dysfunctional group" (DYS), the "interpersonally distressed" (ID) group, and the "adaptive copers"(AC) on the basis of responses to the Multidimensional Pain Inventory (MPI). Overall, Axis I diagnoses were present in 74.8% of the participants with the DYS subgroup mainly reporting anxiety, and the ID group reporting mood disorders. The AC group showed little comorbidity. Axis II diagnoses were present in only 8.7% of the FM sample. This suggested that FM is not a homogeneous syndrome, but shows varying proportions of comorbid anxiety and depression that is dependent on psychosocial characteristics of the patients. Therefore, treatment should focus both on physical and psychologic dysfunction (47). The research completed on the impact of comorbid conditions on FM has shown varied results. A Swiss study has shown the highest rate of comorbidity. In this study of 180 women, FM had 90% comorbidity with psychiatric disorders (48).

Although multiple instruments have been used for the measurement of symptoms of FM, the Fibromyalgia Impact Questionnaire (FIQ) is the most standardized and is widely used. It is an instrument designed to quantitate the overall impact of FM over many dimensions (e.g., function, pain level, fatigue, sleep disturbance, psychologic distress). It is scored from 0 to 100, with 100 being the most severe. The average score for patients seen in tertiary care settings is about 50. The FIQ is widely used to assess change in FM status as well (26,27).

The FIQ is a patient self-rated questionnaire, which consists of 20 separate questions. Of these questions, 11 address functionality and ask about the various activities and instrumental activities of daily living such as shopping, laundry, and household work. Some questions address the impairment in number of days and the extent that symptoms of FM interfered with the ability to do household work. Other questions address the pain, stiffness, anxiety, and depression accompanied with the cardinal symptom of pain. Overall, it measures physical functioning, work status, depression, anxiety, morning tiredness, pain, stiffness, fatigue, and well-being during the preceding week.

MANAGEMENT

Because of the unknown and mixed etiology of FM, there have been multiple pharmacologic and nonpharmacologic treatments used to treat FM, leading to intermediate results. Self-medication is very common among patients with FM. In an outpatient clinic, a survey asking patients with FM regarding the use of Complementary and Alternative Medications (CAMs) for relief of symptoms illustrated that 98% of the patients had used some form of CAM in the last six months. The 10 most frequently used CAM treatments were exercise for a specific medical problem (48%), spiritual healing (prayers) (45%), massage therapy (44%), chiropractic treatments (37%), vitamin C (35%), vitamin E (31%), magnesium (29%), vitamin B complex (25%), green tea (24%), and weight-loss programs (20%) (49).

A recent comprehensive review was published as an attempt to establish guidelines for the management of FM (50). We will draw information from this paper and add the latest updates below. The outcome measures used in most studies mainly include the number of tender points and functionality assessed by the FIQ.

NONPHARMACOLOGIC INTERVENTIONS

In general, the literature on CAM therapy for FM is characterized by small, poor-quality studies that use many different outcome measures. A recent systematic review of FM therapy found that nonpharmacologic interventions were at least as effective as pharmacologic interventions (51).

Patient education seems to be a useful tool, proving to be beneficial for patients in regard to understanding and managing FM. Randomized controlled trials (RCTs) in this area have shown that education with the help of written material and group discussions improves pain, fatigue, sleep, and functionality (i.e., walking), anywhere between 6 and 17 weekly sessions have shown to be helpful. The patients who received education and knowledge regarding the illness showed improvement in self-efficacy, FIQ, and the six-minute walk as compared with the control group, which was wait-listed for treatment (52).

Various types of exercises have been used for the treatment of FM, such as high-intensity exercise, aerobic exercise, muscle-strengthening exercise, and pool exercises (aqua therapy). These techniques have shown to be useful in FM patients for decreasing pain and improving functionality (43,53–60). A systemic review of all exercise trials (61) for FM suggested that there is often improvement in aerobic performance, tender point pain threshold, and lessening of pain with exercise. Aerobic training is associated with better improvement than stretching exercises alone (62,63). Addition of education regarding FM tends to be more helpful than exercise alone or being on a treatment waiting list (52). Aerobic training and biofeedback as a combination were also more effective than the nontreated control group (64). Meditation, relaxation, and stress management (65–67) have been shown to be helpful for pain improvement in FM patients. The above suggests that multimodal treatments may have the greatest effect.

RCTs of cognitive behavior therapy (CBT) with longitudinal data over 6 to 30 months found statistically decreased pain severity and improved functioning in FM (68–71). Systematic reviews have confirmed that CBT may improve all four components of FM (pain, fatigue, mood, and function) (72).

There is strong evidence that multidisciplinary treatment is effective in treating FM and theoretically has the best response rates. Five RCTs of multidisciplinary treatment that combined education, CBT, or both with exercise were found beneficial for patient self-efficiency, significant decreases in pain, and improvements on a six-minute walk (52,59,60,65,73,74). One study observed the effects of six-week biofeedback therapy in combination with education, CBT, and exercise and found that the combination of treatments is better than the education control group on self-efficiency and tender points (64). Positive changes have been noted in pain severity, FIQ, self-efficiency, and the six-minute walk as well (68,69,75–78). After treatment, the beneficial effects seen with this multimodal treatment strategy were maintained in three out of five trials over a period of two years. In one key study, 43 patients were given a combined intervention in the form of a rheumatologist and physical therapist intake and discharge, 18 groups of supervised exercise therapy sessions, 2 groups of pain and stress management lectures, 1 group education lecture, 1 group dietary lecture, and 2 massage therapy sessions (79). The intervention group showed improvement in self-perceived health status, average pain intensity, pain-related disability, depressed mood, days in pain, and hours in pain, but no significant differences in non-prescription drug use, prescription drug use, or work status. These changes were maintained over 15 months again suggesting the long-term effectiveness of multidisciplinary therapy.

Other therapies such as qigong therapy with body awareness have been tried, but no positive effect was found on FM symptoms and functioning (80). Eye Movement Desensitization and Reprogramming (EMDR) in an open trial of only six patients helped the relaxation process when other relaxation processes failed (81).

PHARMACOLOGIC MANAGEMENT

At least three meta-analyses have looked at the efficacy of TCAs for FM. The results are mixed with two meta-analyses suggesting that they do improve most of the symptoms of FM, while one suggested that even though the symptoms improved, the functionality of the patients did not show any improvement (82). A meta-analysis (83) confirmed trial data and concluded that TCAs, particularly in low doses (25–50 mg/day), were effective for improving pain, sleep, fatigue, and depressive symptoms of FM, with 25% to 37% of patients tending to show improvement in symptoms. Most of the studies in this analysis lasted from 6 to 12 weeks of treatment. A second meta-analysis suggested improvement in all symptoms except tender point pain with low-dose amitryptiline (83). A third review of medication use for FM included seven amitryptiline, two dothiepin, one citalopram, one 5-hydroxytryptophan study, and two fluoxetine studies, showing that although medication was useful for improving physical status and FM symptoms, overall functionality did not improve despite medication use (84).

Mechanistically, tricyclics may work as noted earlier, in that they promote SR/NE activity in descending spinal pathways, which activate GABA interneurons, which then directly inhibit spinal afferent pain neurons from firing (44). The tricyclics are also known to block sodium channels. Perhaps this lends to their cardiotoxicity at higher doses, but at lower doses, some of this sodium channel blockade may dampen segmental pain firing similar to antiepileptic and antineuropathic medications (44).

Among the newer antidepressants, fluoxetine, sertraline, venlaflaxine, and duloxetine have been shown to have moderate effectiveness for treating FM pain (85,86). Duloxetine now has FDA approval for treatment of FM. SNRIs such as duloxetine treat MDD by increasing the amount of available SR and NE at the synapse in cortical and subcortical structures to treat depression and anxiety, while greater NE and SR availability in spinal cord synapses explains the mechanism involved in treating "the diabolical learning of fibromyalgia" and central sensitization. The dosages used for the fluoxetine and duloxetine tended to be higher (80 mg/day and 120 mg/day, respectively). Lower dosages, such as 20 mg of fluoxetine, were found to be not as effective. Venlaflaxine at high doses (>150 mg/day) was helpful for FM (87,88). A combination of fluoxetine (20 mg/day) and cyclobenzaprine (10 mg/day) seemed to help better than either agent alone (89).

Mirtazapine, a noradrenergic, serotonergic, and histaminergic antidepressant, improved FM symptoms in more than 40% of patients in open trials, but the results have yet to be replicated in controlled trials (90). As the improvement in symptoms of FM coincided with improvement in symptoms of depression, a common pathophysiology of these two may be possible. Of the patients treated with Milnacipran, (which is a highly noradrenergic SR-NR reuptake inhibitor available in Europe), at 200 mg/day, 75% reported overall improvement, compared with 38% in the placebo group; 37% of twice-daily milnacipran-treated patients reported at least 50% reduction in pain intensity, compared with 14% of placebo-treated patients ($p < 0.05$) (91). This drug has now received FDA approval for FM treatment in the United States; approval from the EMA in Europe is pending.

A randomized, placebo-controlled, double-blind, parallel-group, multisite, 12-week study of duloxetine monotherapy in FM tested the safety and efficacy of both 60 mg twice daily and a lower dose of 60 mg once daily versus placebo in 354 women with FM with or without current MDD (92). This study included only women to confirm the results of a previous duloxetine trial in which women, but not men, responded significantly to duloxetine compared with the same-sex placebo-treated patients on efficacy measures (86). The primary outcome measure was pain severity as measured by the Brief Pain Inventory (BPI) average pain severity score (score range 0–10). Compared with the placebo group, the duloxetine 60 mg daily group and the duloxetine 60 mg twice daily group experienced significantly greater improvement in the BPI average pain severity score, beginning at week 1 and continuing through week 12. Significantly more patients treated with duloxetine 60 mg daily (41%) and duloxetine 60 mg twice daily (41%) compared with placebo (23%) had a ≥50% reduction in the BPI average pain severity score. Compared with placebo, duloxetine 60 mg daily or duloxetine 60 mg twice daily resulted in significantly greater improvement in the remaining BPI pain severity and interference scores, and other secondary outcomes, including the FIQ, Clinical Global Impression of Severity, and the Patient Global Impression of Improvement. Consistent with the first duloxetine study, several quality of life measures significantly improved in both duloxetine groups compared with the placebo group, including the quality of life in depression scale total score, the Sheehan Disability Scale total score, and the SF-36 mental subscore, bodily pain, mental health, role limit emotional, role limit physical, and vitality. There were no significant differences between duloxetine 60 mg daily and duloxetine 60 mg twice daily treatment groups in efficacy outcomes. However, only the

duloxetine 60 mg twice daily dose, compared with placebo, significantly improved the tender point assessments. This suggests that the higher dose may be necessary to improve pressure pain thresholds, which have been found to be less responsive to treatment in previous FM trials using tricyclics (82,83). As in the first study of duloxetine, the treatment effect of duloxetine on pain reduction was independent of the effect on mood and the presence of MDD.

Another tricyclic compound, cyclobenzaprine (10–40 mg/day), which is used as a muscle relaxant, has been shown in multiple RCTs (93,94) and one meta-analysis (95) to be fairly effective for symptoms and functionality in FM. The improvement was not maintained over a period of six months for any of the tricyclic agents in limited studies (93).

There was a recent large RCT performed evaluating gabapentin for FM. This was a three-month trial. The number of patients enrolled was 150, and a therapeutic response was defined as 30% decrease in the BPI score. There was an average difference of approximately one point at 12 weeks in the BPI between placebo- and gabapentin-treated patients. In global improvement at week 12, 70% of gabapentin-treated patients rated themselves as better, while only approximately 35% of placebo-treated patients rated themselves as better. The dosing was naturalistic and varied from 1200 to 2400 mg maximum daily dose. Gabapentin is a possible analog of the neurotransmitter γ-aminobutyric acid (GABA), and exerted robust analgesic and antiallodynic effects in syndromes secondary to central sensitization of pain responses (96,97), but had minimal effects in models of acute, transient pain (98). Taylor et al. (99) suggested that gabapentin did not appear to reduce immediate pain from injury, but appeared to be effective in reducing abnormal hypersensitivity (allodynia and hyperalgesia) induced by inflammatory responses or nerve injury. The antinociceptive effects of gabapentin are more accurately hypothesized to be mediated by modulation of calcium channels via $\alpha 2$ delta ligand binding, modulation of transmission of GABA, and possibly other additional unidentified mechanisms (100). In addition to a drop in pain, sleep also improved, indicating gabapentin may be helpful for multiple modalities of FM symptoms.

Pregabalin, a simple molecule, was the first FDA-approved drug for FM. A study looked at the efficacy of pregabalin treatment for the pain and anxiety component of FM (101). The proposed mechanism of action for pregabalin is the selective blockade of calcium channels, similar to gabapentin, resulting in a decrease in glutamate release and decrease in sensitization in the CNS. Pregabalin at 450 mg/day significantly reduced the average severity of pain in the primary analysis compared with placebo ($\sim$0.93 on a 0–10 scale) ($p < 0.001$), and significantly more patients in this group had >50% improvement in their pain diary scores at the end point (29% vs. 13% in the placebo group; $p < 0.003$). Pregabalin at 300 and 450 mg/day was associated with significant improvements in sleep quality, fatigue, and global measures of change. Pregabalin at 450 mg/day improved several domains of health-related quality of life. Dizziness and somnolence were the most frequent adverse events. Rates of discontinuation due to adverse events were similar across all four treatment groups. Pregabalin at 450 mg/day was efficacious for the treatment of FM, reducing symptoms of pain, disturbed sleep, and fatigue compared with placebo. Pregabalin was well tolerated and improved global measures and health-related quality of life. Efficacy was noted as early as first week. This was an eight-week study, and two of the key domains, sleep and pain, showed better

overall improvement. Only women participated in this study. Also, approximately 30% of pregabalin 450 mg treated patients had ≥50% reduction in pain versus 13% in placebo. And approximately 50% of patients had a partial response reduction in symptoms by 30% per pain diary scores. Patients were told to stop antidepressant treatment, and therefore, patients with more severe affective symptoms would have dropped out or chosen not to participate in this study. The most common side effects were somnolescence and dizziness.

In RCTs, tramadol that has a built in SNRI component (20–300 mg/day), with or without acetaminophen has been shown to reduce FM pain (102,103). In the long-term treatment of FM, NSAIDS have been found useful only in combination with TCAs, and monotherapy results have been disappointing (104). This suggests a neuropathic etiology for FM instead of an inflammatory or nociceptive one. There is no controlled data on the use of opioids for FM, although they are sometimes utilized as tertiary treatment. Most of these successful studies targeted and improved pain and tender points. Recent imaging studies show occupied opioid receptors in drug naïve FM brains and suggest that opiates may not work well.

In an open trial using the second-generation antipsychotic, olanzapine for FM symptoms, tolerability was poor, with 44% discontinuing the medication, mainly because of weight gain. However, 6 out of 14 patients who completed the trial showed improvement in symptoms (105). Again, controlled trials are needed to validate the use of atypical antipsychotics in FM because of high incidences of metabolic side effects seen from medications. Theoretically, quetiapine with its NRI metabolite or ziprasidone with its SNRI component may have the best chance (44).

Tropisetron (SR antagonist) and SR precursors, have successfully shown improvement in symptoms of FM in three RCTs (106–108). *S*-adenosyl-L-methionine (SAMe) showed improvement in one RCT (109) but was equivalent to placebo in another study. Women with FM with low insulin-like growth factor (IGF)-1 levels experienced an improvement in their overall symptomatology and number of tender points after nine months of daily growth hormone therapy. This suggests that a secondary growth hormone deficiency may be responsible for some of the symptoms of FM (94). Also as delta sleep decreases, so does the ability to be more resilient to our emotions and modulate responses to stresses throughout the day. γ-Hydroxybutyrate has been shown to be useful for improvement in fatigue and pain in one RCT. It causes an increase in slow-wave sleep and decrease in the severity of alpha sleep intrusions in FM patients. It is also likely that delta sleep improves human growth hormone, which is restorative in nature for connective tissues (110). Thyroid hormone, dehydroepiandrosterone, melatonin, calcitonin dietary modifications, nutritional supplements, magnesium, herbal therapy, or vitamin therapy do not have sufficient data to comment on their efficiency in FM (111). Prednisolone and guanefesin have shown to be noneffective for FM (112).

Intravenous immunoglobulin injections for chronic pain were useful in reducing more than 70% of the pain in one out of five patients with multiple pain syndromes (113). Well-controlled studies focusing only on FM patients are needed to further validate its use.

There is some evidence to support the use of relaxation techniques, biofeedback, and hypnosis in patients with FM. Eight sessions of hypnotherapy delivered over 12 weeks allowed for improved pain ratings, fatigue, sleep, and

global assessment (114). A study using hypnotically induced analgesia found that patients experienced less pain during hypnosis than at rest (115). Electromyogram biofeedback was moderately effective in decreasing pain ratings and tender point counts (116,117). One study showed that hydrogalvanic baths and relaxation therapy did not help sleep and pain in FM patients (118). There are no RCTs using trigger-point and tender point local anesthetic injections in patients with FM.

A review of seven studies using acupuncture in patients with FM reported increased pain thresholds, decreased pain ratings, and decreased medication use with acupuncture treatment (119). These results are often mixed with some trials showing acupuncture to be helpful (120,121).

Chiropractic spinal manipulation and soft tissue massage decreased tenderness in patients with FM (122,123). Both of these were open trials and only the massage trial had a comparison group. Connective tissue manipulation and massage had produced positive results by reducing depression, pain intensity, and amount of analgesics used (123). A combination of diathermy ultrasound and inferential current improved pain levels and sleep compared with sham treatment (124). An Israeli RCT concluded that medicinal baths (Dead Sea sulfur baths) resulted in relief of FM-related symptoms of pain, fatigue, stiffness, and tender points (125). One review suggested that spa therapy would be useful as an adjunct to conventional treatment in FM patients (126).

CONCLUSIONS

To summarize, there is strong evidence to support the use of low-dose tricyclic medications, such as amitriptyline and cyclobenzaprine, as well as cardiovascular exercise, CBT, patient education, or a combination of these for the management of FM pain. There is moderate evidence that tramadol, SSRIs, SNRIs, sodium oxybate, and certain anticonvulsants are effective, but the studies for newer agents are still ongoing. We have three FDA-approved drugs for FM—pregabalin, duloxetine, and milnacipran—suggesting a stringent evidence base for these three individual treatments. Moderate evidence also exists for the effectiveness of strength training exercise, acupuncture, hypnotherapy, biofeedback, massage, and warm water baths. As mentioned above, it appears that combinations of many modalities may offer the best treatment options and outcomes for patients with FM.

Controlled trials exist and suggest that some approaches are significantly beneficial. Furthermore, the finding that multiple treatment modalities targeting various areas of life including the biologic, psychologic, and social aspects are needed to reasonably treat FM patients, and this leads one to theorize that FM has a complex multifactorial etiology, possibly comparable to the biopsychosocial model often employed in treating MDD and other psychiatric illnesses. With regards to treating FM in psychiatric practice, the authors offer the following explanations and suggestions.

Borrowing from the thoughtful pharmacodynamic theory work of Stephen Stahl (127–129), there may be some underlying neurocircuitry malfunction associated with the production of key symptoms in fibromylagia. For example, fatigue, lethargy, and poor concentration are symptoms often associated with both FM and MDD. Both disorders are complex in symptom variability and heterogeneity and etiology. In MDD, the underfunctioning of the NE system is

felt to create some of these depressive symptoms. The corollary exists then, that a noradrenergic-enhancing antidepressant may be able to reverse fatigue, for example, as this neurocircuitry is enhanced, which controls this target symptom and MDD may be alleviated. If such an antidepressant could help fatigue associated with MDD, then it is possible that the same CNS mechanism or circuit is underperforming in FM-induced fatigue, and facilitating it may be helpful in treating FM as well. Evidence above suggests that NE-enhancing SNRIs are helpful here. Another neural circuit of interest may be that of histamine, which projects to the frontal cortex where executive functioning and perception of arousal state occur. CNS facilitation by presumably prohistaminergic drugs, like modafinil, may treat fatigue associated with multiple medical conditions (obstructive apnea, Parkinson's disease), which may lend to its use in the treatment of FM fatigue in a similar manner, and a naturalistic paper by one of the authors shows modafinil to have success at treating some of the cognitive problems, or "fibro fog" as well as the fatigue of FM (130–132). This example of using pharmacodynamic knowledge, that is, the perception of fatigue is not only dependent on peripheral stimuli but also the psychologic threshold of the person to manage with fatigue, and the brain's ability to interpret fatigue, could be useful to help reduce FM fatigue symptoms by increasing NE or histamine transmission. This approach would allow the clinician to choose complex medication regimens to reverse specific target FM symptoms comparable to our approach in MDD patients. Finally, instead of trying to promote wakefulness and appropriate energy during the daytime in FM as above, one could address the relative lack of slow wave, deep sleep in these patients at night and utilize an agent, such as sodium oxybate, which has been shown to improve morning alertness and quality of sleep in patients with FM. This agent has controlled trials in FM to support its use (110,133). Again, one may use a different drug on a different set of neural circuits to allow better sleep (antihistamine products or GABA-enhancing sedatives) and improved energy in FM as well, though there is less evidence here in the literature. This well-thought-out combination of medications is "rational polypharmacy" for some patients. This approach is widely accepted in treating MDD for reasons noted above and should strongly be considered when treating FM as well.

In regard to pain management, the same principles as fatigue management may be applied. There is reasonable controlled data showing that some forms of physical therapy are helpful in treating pain associated with FM. Assuming this is one of the safest treatments discussed, exercise is a good starting point for any clinician. If physical therapy fails to gain remission from FM symptoms, then an evidence-based approach, which utilizes a second treatment modality, not clearly related or overlapping with exercise, might occur next. For example, instead of adding aerobic exercise one could try CBT or biofeedback if available. Another path might lead toward medication where good data exist in that adding a tricyclic or an SNRI, such as duloxetine, to facilitate SR and NE may make logical sense. These drugs facilitate two neurotransmitters, which are felt to be effective in either decreasing the peripheral pain signal upon entry to the CNS or allowing the brain to interpret these signals in a less severe manner. Again, the patient now has an exercise-based approach and a nonoverlapping pharmacodynamic approach to treating their FM. If the patient is still failing to reach remission from the FM target symptom of pain, then another additive approach could include the use of an antiepileptic/nociceptive agent such as pregabalin to dampen

peripheral pain signals via calcium channel modulation or to use tramadol to dampen pain via an opiate-like response. Again, the theory is to use rational polypharmacy, where medications with nonoverlapping mechanisms are added together to obtain an additive or synergistic effect. This practice, again, is similar to that used in treating MDD to full remission. However, the average psychiatrist may have to increase his or her comfort level in using some of these nontraditional "psychotropics" and also get used to using more off-label prescribing practices after assessing the literature available to support these practices.

Oftentimes, the psychiatrist is not the primary provider for the FM patient. Psychiatrists are often asked to consult to rule out psychopathology and provide treatment if any exists. Certainly if there is a clear and comorbid mental illness, this is the domain of the psychopharmacologist, and usual practice guidelines should be followed for the specific psychiatric disorder being treated. However, the pain management aspect of care is often delegated to the primary care physician or rheumatologist. If this is the case, one may not delve completely into the rational polypharmacy practices noted above, but should continue to treat any axis I/II conditions aggressively either with usual monotherapy or polypharmacy as needed. We suggest that psychiatrists challenge themselves and their countertransference toward these "somatic" patients who are often difficult to manage. There are clearly patients with FM who do not have any psychiatric comorbidity who develop depression, anxiety, regression toward axis II conditions as a response to intractable pain and social dysfunction. There is a group that also develops pain from their primary psychologic condition. Either way, aggressive psychiatric, psychologic, or somatic treatment is warranted. The more complex the case, the more multimodal treatment may be needed. We again, would suggest a target symptom approach whereby each chief complaint symptom associated with FM is addressed. Monotherapy should be strived for, but the willingness for the psychiatrist to set up a good referral network with clinicians who offer these other treatment options or the willingness to gain skill at using these alternative options should be a clear goal in FM patient management.

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17 Depression and Personality

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INTRODUCTION

In usual clinical practice and current nosology, depression is a syndrome defined exclusively by phenomenology. No definite etiology is assumed when assigning the diagnosis. Developmental history, interpersonal functioning, regulation of affect, prior response to treatment, and comorbidities are all necessary inroads that connect the diagnosis of clinical depression with aspects of personality functioning. Once the clinician moves beyond the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) into the context of the case, he leaves the safety of phenomenological certainty for the muddy waters of explanations. In this enterprise, he needs to be informed by theory to screen important information, make etiological conjectures, design treatment, and adjust it as it unfolds. As a guiding tool for this task, our chapter explores the relationship between depression and personality by reviewing a number of arguments and models that emphasize its relevance for diagnosis and treatment.

ARGUMENTS FOR THE RELATIONSHIP BETWEEN DEPRESSION AND PERSONALITY

The design of this chapter follows the structure of an argument. We are trying to demonstrate that depression and personality functioning are better understood and treated together, not separately. Statistical evidence, clinical descriptions, theoretical models, and empirical data are assembled to converge into relevance for treatment.

The Comorbidity Argument

The comorbidity argument is a simple argument in face of the obvious. A recent review finds that 20% to 50% of psychiatric inpatients and 50% to 85% of outpatients with a major depressive episode also have an associated personality disorder (PD), most frequently borderline, avoidant, dependent, or obsessive (1). These numbers suggest that it is very unlikely that the association is a random effect as the independence model (see below) suggests.

The Outcome Argument

The outcome argument maintains that depression and character pathology influence each other's course and prognosis without making any speculation about the nature of the relationship.

Comorbid Personality Disorder Alters the Response to Medications

The introduction of pharmacological treatments for depression in the late 1950s gave rise to therapeutic optimism in this direction. Nowadays, there is enough evidence to show that pharmacological treatment "works." However, in spite of significant progress in neurophysiology and pharmacology, the success remains

limited. Controlled clinical trials show that only two of three patients with depression respond to any given antidepressant, while one in three responds to placebo (2). PDs are largely believed to contribute to treatment resistance, but research evidence is controversial. An early review of studies on the response of depression to tricyclic antidepressants (3) reported that patients with neurotic, hypochondriacal, or hysterical personality traits responded to imipramine or amitriptyline little or no better than to placebo, suggesting that PDs play a negative role in the response to pharmacological treatment. However, the opposite was also found true. For instance, in an eight-week trial of fluoxetine for 83 outpatients with major depressive disorder (MDD), cluster B PDs were predictors of a positive response to fluoxetine (4). Another recent study (5) confirms both of the findings mentioned above. In this six-week study, patients with MDD were randomly assigned to treatment with either fluoxetine or nortriptyline. There were significant differences between depressed patients with and without PD. However, despite these differences, the presence of a comorbid PD did not adversely affect overall outcome, but influenced the response to certain drug type. Thus, patients with a cluster B PD did relatively poorly on nortriptyline compared with fluoxetine. In a 12-week study (6) comparing response to sertraline versus imipramine in chronic depressed patients with comorbid PD, the presence of a PD did not appear to diminish symptomatic response to acute treatment or associated improvement in functioning and quality of life. There were no significant differences between the responses to different classes of medications as related to the presence of a PD. One may speculate about the differential action of antidepressants on the two monoamine pathways involved in depression: serotonin and norepinephrine. For instance, nortriptyline has very little serotonin activity compared with fluoxetine, while sertraline and imipramine are comparable in their serotonin activity. However, mapping PDs on the two monoamine circuits would be simplistic. Moreover, the weakness of these studies is the relatively short period of follow-up, making them relevant only for the immediate response to a pharmacological intervention, and saying nothing about the rate of relapse. In a more psychobiological approach to the problem of PDs and resistance to pharmacological interventions in depression, it was shown that patients with depression who fail to respond to antidepressant treatments have generally higher harm avoidance [one of the four dimensions of temperament confirmed by research along with novelty seeking, reward dependence, and persistence (7,8)] scores before treatment than the others (9).

Comorbid Personality Disorder is Associated with Longer Time to Remission of Depression

In a two-year prospective study that followed the natural course of remission from MDD as a function of PD comorbidity in 302 participants, participants with MDD who had certain forms of coexisting PDs (schizotypal, borderline, or avoidant) had a significantly longer time to remission from MDD than did patients with MDD without any PD (10).

Depression Occurring in the Context of a Personality Disorder May Have a More Severe and Chronic Course

In a sample of 159 undergraduates who experienced at least one prospective depressive episode, cluster C personality disturbance, characterized by anxious

and fearful features, predicted chronicity of depression. Cluster B, characterized by dramatic, emotional, and/or erratic features, predicted severity and duration of depression (11). In a sample of 151 persons with MDD in the community, the presence of a PD was associated with role limitations from emotional problems, social functioning, and general health perceptions (12). In data derived from a six-month trial of fluoxetine and nortriptyline, patients with co-occurring MDD and borderline personality disorder (BPD) ($N = 30$) were more likely to have earlier age of onset of depression, more chronic course, worse social adjustment, more frequent history of suicide attempts, and more alcohol and cannabis comorbidities, compared with patients with MDD without PD ($N = 100$) or patients with other PDs ($N = 53$). Patients with BPD had a worse response to nortriptyline, but not to fluoxetine (13).

Improvement in the Level of Personality Functioning May Lead to Improvement of Depressive Symptoms and Vice Versa

In a study on the effectiveness of long-term psychodynamic therapy for chronic and recurrent depression, anxiety, and PDs, Bond and Perry (14) showed that improvement in overall defensive functioning predicted improvement in observer-rated depression [with a moderate effect size of 0.56 ($N = 29$, $p < 0.05$)]. Even though the study could not determine whether defense change causes symptom change or vice versa or whether both change as a function of some third factor, change in overall defensive functioning was a potent predictor of change in symptoms and functioning. In a three-year longitudinal study of 161 persons with BPD, Gunderson and colleagues (15) reported that improvement in BPD preceded improvement in MDD, but improvement in MDD did not precede improvement in BPD. Remission rate from BPD was not affected by presence of co-occurring MDD. Likewise, Zanarini et al. (16) found in a six-year follow-up study in patients with BPD that patients whose BPD remitted over time experienced substantial decline in all comorbid disorders (mood and anxiety disorders), while those whose BPD did not remit over time reported stable rates of comorbid disorders.

The picture painted above is a composite one, providing a rather confusing image. Indeed, research evidence of the relationship between personality pathology and treatment outcome in major depression as reviewed by Mulder (17) was proved to be inconclusive, as the results seem to depend on study design (what could accurately be said is only that personality pathology does not improve outcome in patients suffering of MDD).

The Etiological Argument

The etiological argument takes the relationship to a deeper level by relating depression and personality dysfunction in terms of causality. One can build this argument by using two venues: *historically developed paradigms* and *logically constructed conceptual models*. The first venue reflects the evolution of the psychiatric Zeitgeist, and a narrative about its history may require the space of an encyclopedia. We may agree to take as a point of reference Freud's seminal 1917 paper—"Mourning and Melancholia" (18)—where Freud discusses about the process of grief and depression as similar yet distinct ways of dealing with loss of an object (significant person). In mourning, the internalization of the loved one as a response to its loss is followed by a slow process of severing

attachments to the internal representation and reconnection with the world, while in melancholia, this process gets stuck because of a high level of ambivalence toward the lost person (an unusual amount of aggression toward the object of love). In melancholia, the internalization of the lost object implies the internalization of a conflict. Instead of the lost person, it is a part of the ego, which receives the aggression and the punishment that the object once received, and mourning is turned into a self-punitive depression characterized by heightened self-criticism, loss of self-respect, and "delusional expectation of punishment." This construct was further elaborated and altered by entire psychoanalytic schools such as ego-psychology, object relations theory, attachment theory, and self-psychology, each emphasizing different aspects of personality functioning. Coming from a different perspective, cognitive theory has been approaching the relationship between depression and personality in terms of schemas, modes, and networks that have cognitive, affective, motivational, and behavioral components (19). In this frame, Beck views depression as a response to loss that activates an "innate program consisting of giving up and withdrawal . . . serves to reduce the individual's needs until new resources were developed" (20). From a psychobiological perspective, Cloninger built a personality model based on four biologically grounded dimensions of temperament (hypothetically related to underlying neurotransmitter systems) and three dimensions of character, which allow to explore those personality factors associated with depressive disorders (9). A rich research literature has been dedicated to this approach.

The other venue to the etiological argument is represented by a number of conceptual models built on logical grounds and supported more or less by empirical research (21–23). Their multiplicity points to the fact that the relationship between depression and personality cannot be encompassed by a single theoretical model.

The Independence Model

The independence model actually refutes the etiological hypothesis maintaining that there is no causal relationship between axis I and axis II conditions. The basic argument of the model is that the comorbidity is artifactual, that is, generated by a treatment-seeking bias. (For instance, the co-occurrence of depression and a PD increases the likelihood of a person to seek treatment.) There are no data to support this statement. A more interesting way to prove this model is the evidence that occurrence of treatment-resistant depression is not related to the presence of a PD as shown in a study by Petersen et al. (23,24). Yet, many more studies support the relationship (see also section "The Comorbidity Argument"). Even though it is not well supported by literature, the independence model is useful in that it tells the clinician that a comorbid PD does not necessarily predict a poor response to medications.

The Common Cause Model

The common cause model argues that a shared element between the two conditions is supposed to cause both. For instance, a temperament trait such as high harm avoidance might be a risk factor for both depression and BPD. The same was hypothesized about anxious insecure attachment or about childhood abuse. However, as Klein et al. (21) showed in their review of the model, while logically valuable, such a model is very difficult to test because of methodological reasons

that require the hypothesized causal factor to be clearly defined and measured before the onset of either condition. Besides, depression and personality would have to be clearly defined and measured as distinct constructs, and independent linkages from the common cause to each of the hypothesized effects should be specified and established either from experimental or correlational designs. Furthermore, the possible interaction between the two processes (see the other models discussed below) and the probable multifactorial etiology of each are likely to complicate the picture.

The Spectrum and Subclinical Model

The spectrum and subclinical model maintains that the axis II disorder is a milder version of the axis I condition. For instance, schizotypal, paranoid, and schizoid PDs might be part of schizophrenia spectrum even though supporting evidence is not very strong (23). In the same vein, depressive personality, dysthymia, and major depression might be seen as parts of the same continuum (25). Those who maintain this position claim that psychological distress, as manifested by elevated levels of depressive symptoms (e.g., dysthymia), is continuous with clinical depression. A different position holds that major depression is a distinct clinical entity. For instance, Santor and Coyne (26) found that depressed mood, anhedonia, and suicidality were more likely to be expressed in clinically depressed than in nondepressed individuals, whereas hypochondriasis and middle insomnia were more likely to be expressed in nondepressed individuals at similar levels of severity. They claim that such qualitative differences are inconsistent with the view of depression as a simple continuum.

The Predisposition-Vulnerability Model

The predisposition-vulnerability model applies to the situation when the possibility of having one condition predisposes an individual to develop the other. It is intuitive that a PD may predispose a person to depression, but it is also possible that depression early in life may facilitate the development of a PD. The predisposition-vulnerability model is consistent with *the stress-diathesis model*. Stressful life events are known to precipitate major depression. However, it remains unclear why some individuals who experience adverse events develop depression, whereas others do not. A step toward an explanatory mechanism about how a certain vulnerability predisposes to depression is the *congruency model* (25). It alters the stress-diathesis model by referring not just to any kind of stress in a context-independent manner, but to those specific life events that are congruent to the preexisting vulnerability. The hypothesis assumes a connection of meaning between the quality of the stress and the vulnerability. Areas of vulnerability studied in the literature in relation with depression have been loss of a parent in childhood, being raised by a depressed parent, insecure attachment, etc., and how the occurrence of life events affects treatment outcome. For instance, individuals with a dependent type of character are supposed to be more vulnerable to experiences of loss or separation, while self-critical people are more likely to get depressed in situations of failure and lack of accomplishment. The results of empirical research verifying this hypothesis are reviewed elsewhere (27) and show that the hypothesis does not uniformly apply. While people with dependency traits are more vulnerable to negative interpersonal events, the self-critical individuals are sensitive to a wider range of

events other than failure. An extension of the stress-diathesis model to an *action theory model* emphasizes that individuals may actually generate the kind of stress they are vulnerable to, a mechanism reminding of Freud's repetition compulsion (28). Dependent people, especially in the borderline range, generate emotionally charged relations that frequently end in separation, whereas self-critical individuals with unreasonably high internal standards set themselves up for failure. The concept of *active vulnerability* by which individuals generate contextual risk factors that increase the likelihood of depression is useful here.

The Pathoplasty-Exacerbation Model

The pathoplasty-exacerbation model implies that the presence of one disorder influences the course of the other. For instance, depression exacerbates the social isolation of people with avoidant character, thus further worsening depression. The effects can be additive (pathoplasty) or synergistic (exacerbation) (23,29).

The Metaphor Model

The metaphor model is our addition to the picture. It has not been the subject of extensive study because metaphors, while being clinically useful, cannot be converted into invariant research constructs. Their fate is never sure, as they may go out of favor from one session to the next, but even then metaphors can make an indelible mark on one's memory. "The battled-fatigued mother syndrome of either gender," "the parentified child syndrome," "the burnt-out family hero," or "the demoralized scapegoat"—all coming from the symbolic experiential family therapy repertoire of unproven disorders (David Keith—*A Guide to Family Interviewing*, unpublished)—are literary forms that sometimes do more justice to the complexity of a case than a psychiatric diagnosis. Metaphors do not only take a symptom like depression in the context of a personality, but embed the personality altogether in a plot that may end up for them like Hamlet, Anna Karenina, or Charlie Brown. Within such a model, the clinician is given permission to alter the script. A hybrid form between research model and metaphor is a medical metaphor on the relationship of depression with personality as seen by Peebles-Kleiger (30):

> Depression is similar to fever. Although it is treated in its own right when it threatens well-being, it is also understood to be a signal for the presence of one of a number of psychological dysfunctions. For example, depression could be caused by protracted grief, chronic low-grade hopelessness generated by childhood trauma, deficits in managing being alone, guilt over squelched aggressive impulses, or a chronic sense of emptiness despite one's outward adaptation. Each of these dysfunctions requires a different therapeutic strategy.

The Taxonomic Argument

The taxonomic argument is a consequence and a refinement of the etiological argument, and it is based on various models depending on whether the emphasis falls on depression or personality. Approaching depression in the context of personality functioning has led to description of types, thus introducing depth into the picture. For instance, Blatt (25,31) describes two research-supported types of depression—anaclitic and introjective—reflecting a developmentally built vulnerability to either abandonment or self-criticism (see

also section "Depressive Personality"). Along the same lines, but from a cognitive perspective, Beck (32) describes a sociotropic and an autonomous type of depression. Using an interpersonal model, Arieti and Bemporad (33) discuss three patterns that cause vulnerability to depression: (*i*) dominant other, (*ii*) dominant goal, and (*iii*) self-denying.

The other way to build this argument is to take each type of PD as a point of departure and explore its venue(s) to depression. In what follows, the order of presentation of PDs does not follow exactly the DSM-IV cluster order. Some types of PDs such as self-defeating and depressive do not appear in the last editions of DSM but are reified as categories in the more recent enterprise of the *Psychodynamic Diagnostic Manual* (34). We choose to include these types for their clinical relevance. Some other categories such as avoidant and dependent are presented under the category of depressive personality.

Antisocial Personality Disorder and Depression

The psychopathic character is not naturally predisposed to depression, as grandiosity is used as a defense (35). It deals with feelings by either suppression or acting out. Its core affective themes are rage and envy. However, even psychopathic characters can get depressed when by reasons outside of their own power they lose their persona. These conditions, may they be illness, aging, imprisonment, or loss of status, can lead to an experience of depression, which is aggravated by the fact that antisocial subjects associate ordinary emotions with weakness and vulnerability. Comorbid substance use and impulsivity increase the suicidal risk in this category (36). On the other hand, as one earlier study showed, the presence of depression seems to improve treatment outcome in antisocial patients with opiate dependence by making them more amenable to psychotherapy, even though the behavioral manifestations of sociopathy are present (37). An explanation for this observation may be that in a depressed state, the antisocial is able to take more responsibility for mistakes and for needing help, instead of assuming a grandiose self.

Paranoid Personality Disorder and Depression

The paranoid character lives in a state of hypervigilance of attacking/being attacked by others as a result of a defense strategy in which one's aggressive wishes are dealt with by projecting them onto others. Thus, the disowned attributes are turned into external threats. Such a defensive style is costly and may lead to burnout and depression. The predisposition-vulnerability model seems to apply in this case (23).

Schizoid Personality Disorder and Depression

The organizing theme of schizoid personality is the high sensitivity to interpersonal stimulation that is dealt with by affective and physical withdrawal from the world and subsequent suppression of emotions (38). Schizoid people prefer distance, being "on the outside looking in," but can reach a point where detachment from the world and suppression of emotions result in emptiness, meaninglessness, and depression. Depressive withdrawal further aggravates the schizoid pattern, making reward from reconnection to the world, and from interpersonal relations even less possible. The pathoplasty-exacerbation model seems to apply in this situation.

Borderline Personality Disorder and Depression

Clinical depression is extremely common in BPD, occurring in over 90% of patients (14). Given this high rate of co-occurrence, the question arises whether depression is an inherent component of BPD consistent with the common cause model or vulnerability-predisposition model? The two major longitudinal studies cited above (13,14) suggest that this is indeed the case. Over time, recovery from MDD and other axis I disorders is predicted by recovery from BPD, and not vice versa. In addition, there is some evidence that depression has a different pathophysiology when it co-occurs with BPD, including a different profile of gene expression, and a worse response to usual treatments (39–41). Moreover, studies comparing the quality and phenomenology of depression with or without co-occurring BPD have indicated that when BPD is present, MDD is accompanied by feelings of emptiness, loneliness, and longing for attachment figures (42–44). These characteristics have a negative correlation to depression severity in patients without BPD (43).

Object relations and attachment theories provide a means of explaining these research findings. Attachment theorists have postulated that human infants have a primary need for an attentive and nurturing mother (45). In their research of persons with BPD, Fonagy and Target (46) noted that such persons become preoccupied with seeking an idealized mother figure. They hypothesized that this pathological attachment seeks results from a previous history of inadequate attachment with mother during infancy. Employing an object relations perspective, Kernberg (47) also noted pathological dependency in persons with a borderline level of personality organization and tied it to split attributions of idealization and devaluation. Kernberg hypothesized that pathological dependency results from a "search for the gratification of an idealized mother image, which is completely split off from the dangerous, threatening mother image."

Consistent with the research findings by Fonagy and Target, Gregory (48) explained that patients with BPD enter a depressive state called the guilty perpetrator state in response to separation fears. In their longing to maintain idealized attachment, he postulated that such patients sacrifice their own autonomy and self-esteem. They conform to the needs of the other person, take on all the responsibility for anything that goes wrong in the relationship, and become the bad person, to maintain an idealized image of the other. Self-destructive behaviors, such as cutting or overdose, serve as a form of atonement for self-perceived badness and thus relieve dysphoria. They also serve to displace aggressive impulses that might otherwise jeopardize a relationship.

Gregory outlined specific methods to deconstruct this depressive state as part of a treatment labeled *dynamic deconstructive psychotherapy*. In a recent randomized controlled trial, this treatment was very effective in reducing depressive symptoms and suicide-related behaviors for patients with co-occurring BPD and alcohol use disorders (49).

Depressive Personality and Depression

Even though the depressive PD was relegated to the appendix of DSM-IV, in the empirical research studies of Shedler and Westen (50) depressive personality appears to be the most prevalent personality structure. The authors maintain that "the composite descriptions of avoidant and dependent PDs overlap

substantially and contain numerous features that may be better characterized in terms of a depressive or dysphoric personality syndrome (e.g., the tendency to feel unhappy, depressed, despondent; to feel inadequate, inferior, or a failure; to blame themselves for bad things that happen; to be inhibited about pursuing goals or successes; to feel ashamed or embarrassed; to fear rejection and abandonment; etc.)." This category was reintroduced in the *Psychodynamic Diagnostic Manual* (34) with two subdivisions according to an object-relational and cognitive-developmental point of view. Blatt (25,31) described dependency and self-critical perfectionism as major vulnerability factors for depression, resulting in two distinct types of depression: *anaclitic* (dependent) and *introjective* (self-critical). The term "anaclitic" was initially derived by Freud (51) from the Greek word *anaclisis*, meaning to lean on. The *anaclitic depression* has as core themes fears of abandonment, neglect, and not being loved together with desire to be fed, comforted, and protected. Main affects are helplessness, weakness, and depletion, while guilt is minor. The anaclitic-depressive personalities show high dependency needs, their relationships are based on need gratification/frustration, and alternate between blissful union and utter depletion. They have relatively little capacity for internalization of experiences of gratification and difficulties tolerating delay in gratification. Their poor object constancy results in incapacity to tolerate object loss and continuous demands for the constant visible and physical presence of objects. Hypomanic reactions are defense mechanisms used to minimize the effect of object loss while frantically seeking replacement sources of gratification. The *introjective depression* presents at core with excessively high internal standards, proclivity to assume blame and responsibility, a sense of internal badness, and expectation of punishment. The core affects are guilt, self-doubt as well as concerns with atonement, and forgiveness. The developmental origins of this depressive dynamic are found in markedly ambivalent, demanding, deprecatory, and hostile parent-child relationship that are introjected (internalization of the aggressor) and create an ambivalent sense of self. Relationships are not sought for gratification but for approval and acceptance. These people tend to be highly ambivalent and unable to resolve and integrate contradictory feelings. As compensation of the internal pressure thus generated, the introjective depressives focus on achievement, working to seek approval and minimize failure to the point of losing the capacity for enjoyment.

Self-Defeating (Masochistic) Personality and Depression

Self-defeating PD is part of the depressive disorder spectrum but displays some specific dynamic features and treatment requirements that justify its approach as a separate category. Sensitivity to rejection and loss, inferiority feeling, unconscious guilt, inhibition of unconscious anger at others are common to both depressive and self-defeating characters. Yet, self-defeating people are usually taking a more active stance in face of depression. They also can feel anger and indignation in a way resembling those with paranoia. However, in face of attacks on their self-esteem the paranoid usually attacks the other first, while the masochistic response is a preemptive attack on the self: "I'll attack myself so you don't have to do it!"—a dynamic called "passive-into-active transformation" (38). Two variants of masochism were described. The *moral masochistic* personalities build their self-esteem on suffering, by claiming a moral superiority to

those who cannot endure as much. They belong to the introjective side of the depressive spectrum. The *relational masochists* dwell on the belief that suffering is necessary to maintain relationships. They are more anaclitic and usually function at a borderline level. Patients who self-mutilate or get involved with strangers at moments of perceived unavailability of their therapist usually belong to this subcategory. One observation not yet supported by research phenomenon is that pharmacological and psychological interventions that typically relieve depression tend not to work with masochistic characters.

Narcissistic Personalities and Depression

Narcissistic personality is associated with early onset of major depression (52). However, the latter may improve the treatment outcome of the former. According to psychodynamic theory, the narcissistic personality is viewed as built around a frail sense of identity and self-esteem. Subjects with narcissistic organization experience an inner sense of and/or terror of insufficiency, shame, weakness, and inferiority, which they defend by attitudes of self-righteousness, pride, contempt, self-sufficiency, vanity, and superiority (38). Being treated as children not for what they really were but for the function they fulfilled, the narcissistic subjects manage to develop a false self for purposes of external validation, while fearing that once their real feelings are found out rejection and humiliation will follow. In this unfortunate course of development, narcissistic people become unable to differentiate between genuine feelings and efforts to please or impress others. They need a constant injection of affirmation to feel internal validity, while admiration generates a state of elation and grandiosity. Conversely, the lack of external supplies of self-esteem (self-objects) results in deflation of self-image and subsequent depression, shame, and envy. The *Psychodynamic Diagnostic Manual* (34) describes two kinds of narcissistic personalities—*arrogant/entitled* and *depressed/depleted*—according to their presentation. The former displays obvious entitlement and devaluation, trying to either manipulate or command others, while the latter behaves ingratiatingly, seeks people to idealize, feels chronic envy for the superiority of others, and is easily wounded.

Hysterical/Histrionic Personality Disorder and Depression

The early study of Lazare and Klerman (53) on the association between hysteric personality and depression in inpatient females shows that hysterical personality features, whether or not they predispose to depression, influence the nature and course of the depressive illness. More precisely, the study identifies a reciprocal relationship between hysteric symptoms and certain depressive symptoms such as low mood, helplessness, worthlessness, guilt, and suicidality, while the associated somatic complaints were increased. These findings suggest that hysterical symptoms may protect the patient from a more severe depression. The traits used to define hysteric personality in this study were as follows: demanding dependence, egocentricity, exhibitionism, fear of sexuality, lability of affect, sexual provocativeness, and suggestibility. The authors confirmed the prior observations of Breuer and Freud (54) and Janet (55) about the attitude of the treatment team toward these patients who were regarded as "the bad child," "not sick, just complaining," and not suffering of "true" depression.

Obsessive-Compulsive Personality Disorder and Depression

In a longitudinal study that assessed participants at baseline and at 6, 12, and 24 months, obsessive-compulsive personality disorder (OCPD) showed little or no association with depression or other axis I disorders (56). However, maladaptive perfectionism, one of the criteria for OCPD, has consistently been shown to be associated with depression. Hewitt and Flett (57) describe three dimensions of perfectionism: self-oriented perfectionism (high personal and achievement standards), other-oriented perfectionism, and socially prescribed perfectionism (perfectionism required by other's appraisal) and found that the depressed patients had higher levels of self-oriented perfectionism than did either the psychiatric or normal control subjects. In addition, depressed patients as well as anxious patients reported higher levels of socially prescribed perfectionism than did the normal control subjects (58). The psychodynamic literature links obsessive-compulsive personality traits to a controlling parenting style condemnatory not only of unacceptable behaviors but also of accompanying feelings, thoughts, and fantasies (38). Soenens et al. (59) confirm this theory in a three-wave longitudinal study that links parental control, maladaptive perfectionism, and depression. They showed that parental psychological control at age 15 predicted increased levels of maladaptive perfectionism one year later. Maladaptive perfectionism, in turn, predicted increased levels of adolescent depressive symptoms again one year later and acted as a significant intervening variable between parental psychological control at time 1 and depressive symptoms at time 3. Shame- and guilt-inducing upbringings saturate self-perception and need to be defended against through either isolation of affect (obsessives) or undoing (compulsives). However, in face of high demand, these defenses can be exhausted, and the self becomes vulnerable to guilt and shame and thus depression.

The Therapeutic Argument

The therapeutic argument represents the converging point of the outcome, etiological, and taxonomic arguments. It states that in as much as depression and personality dysfunction are causally connected, the treatment of either one has an impact on the outcome of the other. As mentioned previously, there is evidence that the treatment of PDs improves the outcome of comorbid depression. The implication for clinical practice is complex. Most often the target of treatment is the symptomatic relief of depression through pharmacological means. Addressing the personality-based vulnerability is a skill-demanding and time- and labor-consuming psychotherapy. Understanding that recovery and relapse prevention require a combined treatment approach is an important step toward a successful treatment. What comes next is knowledge about how to combine pharmacology and psychotherapy not just by prescriptive addition but also by theoretically informed integration.

One crucial phenomenon when treating people with PDs is the charged relational aspect that strains the therapeutic alliance. If the clinician attempts to combine medication with psychotherapy, the act of prescribing will be part of the dynamics of therapy. Richard Brockman (60) summarized the issue:

> In a treatment where the same physician is prescribing medication and doing psychotherapy, the common pathway of these forces is transference. Thus, pharmacologic action may modify transference.

And more importantly, because it is less easily recognized, transference issues may affect the patient's subjective experience of the action of medication.

A hysterical, dependent, or anaclitically depressed patient who invests the doctor with the power of a rescuer will likely receive medication as a godsend and respond well. A self-defeating patient who unconsciously doubts the value of feeling well or an introjective depressive patient for whom improving is dependent on perceived self-worth are more likely to respond poorly to medication. The passive-aggressive dependent person will unconsciously displace anger when announcing the provider that his new choice of medication failed to work again. The paranoid and the schizoid patient may resent medications as intrusions and reject them as means by which they feel controlled. If patients unconsciously expect harm to happen in any relationship, they will extend these expectations to the medication offered and likely experience nocebo [a harmless substance that when taken by a patient is associated with harmful effects because of negative expectations or the psychological condition of the patient (Merriam-Webster's online dictionary)] effects (61). Conversely, BPD patients will ask for more medications as a way to fend off overwhelming feelings but also to disengage from the pains of recovery process and therapy work. The prevalence of polypharmacy in BPD patients is symptomatic of this phenomenon (62).

Dynamics like those mentioned above occur with more or less intensity whenever patient and doctor meet and a medication is prescribed. Given the time constraints and the dominantly biological orientation of current psychiatric practice, such dynamics may go unchecked and lead to protracted treatments or treatment resistance. The situation is further complicated when treatment is split between a medication provider and a therapist. The research literature suggests that a personality-centered treatment of depression based on a valid biopsychosocial formulation is most likely to lead to a favorable outcome.

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18 Medication and Psychotherapy Options and Strategies: The Future

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INTRODUCTION

Despite the significant advances that have been made during the last several decades, much remains to be learned about the most effective methods for managing major depressive disorder (MDD). We continue to stand at a point of potentially massive change in our understanding of what are the most effective tools in our psychotherapeutic and pharmacotherapeutic armamentarium, as well as what are the most effective ways to utilize these tools. Several domains that represent the most promising and compelling areas of MDD-focused research are highlighted in the following section.

COMBINING PSYCHOTHERAPY AND ANTIDEPRESSANT MEDICATIONS: SEQUENTIAL APPLICATION

Sequential application of (A) antidepressant first, psychotherapy second, (B) psychotherapy first, antidepressant second and their respected treatment outcomes was explored in our previous book, and there is little new empirical evidence that informs the question of how to optimally combine medication and psychotherapy treatment options. STAR-D has been discussed in at least two chapters of this book in detail and has explored a certain sequence of medication initiatives, but notably has left out atypical, stimulant, and modafinil augmentation on the pharmacotherapy end. This study allowed a cognitive behavior therapy (CBT) switch/augment as well, but this was limited to post-SSRI failure, and interpersonal therapy (IPT) and other manualized psychotherapy treatments were not studied. As described in previous chapters, there is mixed evidence as to whether antidepressant and psychotherapy combination treatment during the acute illness phase actually offers greater efficacy than either modality alone. Factors that account for the mixed nature of this evidence include the patient characteristics of the given study sample, dosing of both antidepressant and psychotherapy treatments, study therapist experience level, and research site (e.g., primary care vs. specialty care). Several studies published during the last 10 years suggest that using antidepressant medication during the acute phase of treatment, followed by the introduction of evidence-based psychotherapy, may confer a better long-term illness course when compared with the traditional acute phase antidepressant/psychotherapy combination treatment. This sequential strategy also potentially offers the therapist more focused treatment targets, in part because the patient has already experienced partial relief from acute phase symptoms. Whether this strategy will prove to be more effective than more traditional strategies is

unknown. Studies with large sample sizes, well-characterized patients, and easily replicable therapies are still needed to draw firm conclusions.

DEVELOPING NEW PSYCHOTHERAPIES

Two new psychotherapies continue to be pioneered, both of which challenge the notion that thought content change is necessary for depressive symptoms to improve. The first is mindful-based cognitive therapy (MBCT) (1), a group psychotherapy developed by Segal and Teasdale, which posits that the way in which patients relate to negative thoughts, rather than alteration of content, is key to effectively treating depressive symptoms. In this treatment, patients are taught to decenter themselves from their negative thoughts and regard thoughts as cognitive events rather than necessary truths. The very limited number of empirical studies that have been conducted suggest that this treatment may be effective in improving long-term illness course, but the jury is still out as a more definitive trial is still in process.

The second such treatment is acceptance and commitment therapy (ACT) (2), developed by Steven Hayes and colleagues. This treatment emphasizes the reduction of avoidant behavior through increasing a patient's awareness of thoughts, feelings, memories, and physical sensations that have been feared and avoided. Clients learn to recontextualize and accept internal events, develop greater clarity about personal values, and commit to needed behavior change. ACT is clearly somewhat different in method than MBCT, but still retains the shift from a focus on thought content alteration to an emphasis on the degree of importance that a patient places on his/her internal state. Like combining medications, which focus on bringing together two or more distinct mechanisms to treat depression, further research might be driven toward combining traditional CBT and ACT. In fact, it would also make sense to evaluate rational polypsychotherapy. For example, would it benefit a patient to (*i*) see an individual and group therapist, simultaneously, (*ii*) see an individual therapist for CBT and another for dynamic therapy, or (*iii*) see an individual therapist for IPT plus CBT?

IPT (3) is less widely practiced than CBT for a variety of reasons. One reason may be that IPT has a less "cookbooky" feel to it than CBT and, because of this, potentially less immediate appeal to practitioners seeking out specialized or advanced training. A second reason may be that IPT has historically been closely tied to biological psychiatry in that depression is viewed, in collaboration with the patient, as a medical illness. It is possible that some psychologists have reacted to this by more closely aligning themselves with CBT and other schools of psychotherapy. Despite this, it is important for efforts to be made to further test IPT as a treatment to help prevent relapse and recurrence and also to determine what the "active ingredients" of IPT are. For this reason, it would be helpful to conduct dismantling studies with IPT.

IPT has increased its evidence base in several areas since our last book was published. Papers exist now in the areas of telephone-based IPT, IPT for adolescents, maternal depression, substance abuse, posttraumatic stress disorder (PTSD), geriatric depression, eating disorders, somatization disorder, depression and cardiovascular illness, borderline personality, bipolar illness, and panic disorder.

It seems that psychotherapies have become more specific and focused in a way that is similar to medications and FDA approvals being specific for indication and application. There is a movement occurring where the thought is not

the type of therapy employed but that the therapist be skilled at core techniques such as empathy and positive patient regard. More work should be conducted regarding what makes a therapist skilled—adherence to CBT or IPT techniques or employing core skills relevant to all therapy types?

Another idea in this direction is a movement toward transdiagnostic or unified psychotherapies where there is less regard for type of anxiety or admixtures of depression and anxiety. The Unified Protocol for the Treatment of Emotional Disorders by Barlow et al. at Boston University is one such model (4). They posit that individuals suffering from anxiety and depression tend to experience negative affect more often and intensely, rather than view these experiences as more aversive. This is a common issue across both anxiety and depressive disorders where these patients have deficits in the ability to regulate emotional experiences owing to unsuccessful efforts to avoid or dampen the intensity of these uncomfortable emotions. These common deficits regardless of specific diagnosis, that is, anxiety subtype or depression, then can become a key target for therapeutic change. This unified treatment aims to increase emotional tolerance, thereby reducing maladaptive patterns of responding to emotions that lead to functional impairment across the emotional disorders.

DISMANTLING AND INTEGRATING TREATMENTS

Neil Jacobson and colleagues, in their groundbreaking study that compared the efficacy of the components of CBT versus the entire CBT manualized treatment package, found that the entire package did not offer any incremental benefit (5). This was a novel idea, and certainly counter to the original treatment methods described by Beck and colleagues. It could be that the behavioral activation component of CBT is just as effective as delivering the entire treatment package, but more research is needed to confirm this. Similarly, treatment that only includes the cognitive components of CBT is worth future study as well. Distilling treatments into their most and least effective components is a worthy endeavor and could decrease the costs of treatments and change the way in which practitioners are trained.

As we know from Garfield and Bergin's seminal text, most psychologists in practice identify themselves as practicing "eclectic" therapy (6). Thus, it is the minority of psychologists on the frontline that adhere to only one school of thought and practice. In parallel with efforts to dismantle known psychotherapeutic treatments, other recent therapy developments have blended conceptualization and methods of existing psychotherapies. Perhaps the best example of this is McCullough's recent development of the Cognitive Behavioral Analysis System of Psychotherapy (CBASP), which represents a creative mix of cognitive, interpersonal, developmental, and psychodynamic techniques (7). Although designed specifically to address the needs of chronically depressed patients, the integration of techniques drawn from different schools into a formal system of psychotherapy is another promising avenue for further research. A larger-scale CBASP study is currently underway as well, and results will help shape future practice in this domain.

Finally, as initially noted in brief, there may be benefit outside of breaking down or developing specific, disorder- and skill-based manualized psychotherapies. There exists a movement that suggests that eclectic or integrated therapies may work well more on the basis of core skills or qualities that a therapist uses, that is, motivation, empathy, openness, collaboration, warmth, positive regard, sincerity, corrective experience, catharsis, establishment of goals,

and establishment of a time-limited approach and that patient effort is needed to effect changes. These skills are also used in manualized and dynamic treatments, and perhaps the quantity and quality of skills used effects positive change regardless of the theory or manual used. Studies in these areas continue as well.

DISSEMINATION OF EVIDENCE-BASED TREATMENTS

A great challenge facing all health care fields is translating research findings to frontline clinical practice. As an example, it is not uncommon for a rural psychologist to have limited access to postgraduate training to keep up to date with current best practices. For many such practitioners, work demands and logistical constraints make it impossible to attend conferences that are typical venues for dissemination of the latest research findings and novel clinical developments. The Association for the Advancement of Behavior and Cognitive Therapies (ABCT), which many regard as the premier organization for practitioners of evidence-based psychotherapeutic treatments for depression, recently reported that most attendees at its annual meeting describe their primary affiliation as an academic research setting. Clearly those most in need of access to research findings and continuing education are not attending this annual meeting in great numbers. Organizations such as AABCT should make outreach efforts to increase attendance of these practitioners and thereby increase dissemination of this knowledge base.

A final area to consider is expansion of the training requirements of all clinical mental health training programs to include greater emphasis on attainment of competence in evidence-based psychotherapeutic treatments for MDD. The obvious starting point for this expansion is increased effort by the American Psychological Association (APA) and the American Association of Directors of Psychiatric Residency Training (AADPRT) to make its accreditation process more stringent regarding this training area. In fact, residency programs are now held specifically responsible for developing competence in cognitive therapy, dynamic therapy, long- and short-term therapy, and medication management and psychotherapy as a starting point. So far there are no centralized guidelines, but training programs must develop their own methodology for training and measuring to a competent level.

Perhaps more so in psychiatry than psychology, we have seen a marked increase in medical education programming and funding. This is due to many reasons. First, pharmaceutical industries are under fire for conflict of interest issues and promoting continuing medical education (CME) events. Second, medical universities are always struggling with the bottom line, and developing and putting on CME events is costly for the faculty member's with respect to both time and finances. Academic pressure if focused on securing grants and royalties, where putting on an educational talk or paper for free is often placed on the back burner. We will need to get better at pulling articles and critically reviewing them on our own, without the experts. PubMed and MEDLINE will save us a trip to the library, and we suggest that clinicians set aside some dedicated reading time, especially if access to CME activities dwindles further.

PSYCHODYNAMIC TREATMENT MODELS: WHAT IS NEXT?

Despite a high degree of intuitive appeal and clinical efficacy in some patients, psychodynamic therapies have lost significant favor as a primary modality for treatment of MDD. In some senses, these therapies have suffered from their

proponents' lack of attention to the completion of rigorous, large-scale studies to establish efficacy. Part of the problem lies in just how to manualize such a treatment and then how to measure therapist competence and adherence. A considerable amount of research work is underway to investigate the therapy process variables that may account for the efficacy of such interventions. This is an intellectually compelling question, but seems to be a secondary research question to be answered. Efforts would be better placed in establishing a network to conduct large-scale trials using a treatment manual that captures what is being delivered in real-world practice settings. In this way, where psychodynamic psychotherapy fits into our menu of treatments for depression will begin to be elucidated.

Similar to CBT and IPT, dynamic researchers continue to also investigate manualized approaches, that is, dynamic deconstructive psychotherapy for borderline personality and alcohol misuse and specific populations where dynamic therapy may lend its effectiveness, that is, major depressive disorder, somatoform illness, and PTSD.

IMPROVING DETECTION OF MDD

Almost every reasonably trained clinician can quote the nine symptoms of MDD. However, the diagnosis may be missed, given the variability and fluctuation of symptoms, as noted in previous chapters. The use of both clinician- and patient-rated scales should continue to be studied, as this may allow better detection and more aggressive treatment to full remission of symptoms. Rating scales may also be employed to detect comorbidity, which is often a key component to resistant MDD. Particularly in the face of busy clinical practices, direct patient entry of scales and information into practice software or web-based applications may allow for real-time data collection, scoring, and documentation. These services exist regionally and often can be modified to clinician preferences. Our practice continues to utilize ClinicTracker software by JAG Products, LLC, which allows us to streamline data collection for both clinical trials and regular clinic visits. This is a paperless system where patients interact with a laptop computer just prior to their visits. Our training clinic has started routinely using the Outcomes Questionnaire-45 (OQ-45) at every visit to assist residents in formulating how they address patient symptoms and issues, and alerting them to areas of strength and weakness in their approaches. Other ideas would include the use of a central Web site and web-based electronic medical records. These often employ data fields that may be used to track patient outcomes. Also, a web-based system may allow patients to log on from home and complete scales in case they felt they were in an impending relapse. Poor scores could be flagged and clinicians alerted. Again, the goal of any of these techniques is to drive more aggressive MDD treatment. More evidence is mounting that routine use of rating scales will increase better patient outcomes, that is, attention deficit hyperactivity disorder (ADHD) and anxiety and depressive disorders. Many of these have been addressed in our previous chapters.

USE OF TARGET SYMPTOM PROBLEM LISTS AND PHARMACODYNAMIC THEORY

This theory is mostly due to the work of Stephen M. Stahl (8), who has spent much time and work pioneering the idea that the key symptoms that overlap in several categorical mental disorders, that is, inability to focus in MDD and

generalized anxiety, and attention deficit disorder, may have a unifying pathological set of dysfunctional neurocircuits. If one cannot focus, then the noradrenergic system may be functioning poorly, and facilitating norepinephrine activity may alleviate the key symptom of inattention in any of these disorders. In fact, noradrenergic medications are FDA approved to treat these categorical illnesses. This would drive the theory of rational polypharmacy or pharmacodynamic theory, where a psychopharmacologist might pick medication based not only on categorical FDA approvals but also on the pharmacodynamic profile of the individual agent that is purported to fix the underlying circuit that will ultimately promote resolution of a particular MDD symptom. This type of advanced pharmacotherapy could promote better symptom resolution, and the same practices may allow clinicians to combine medications for better tolerability as well.

This rational, theory-based approach should be used when the evidence base fails. This often happens in patients with comorbidity or resistant illness, when they have multiple symptoms and are taking multiple medications. For example, there are very few studies on comorbid depression and anxiety and no FDA approvals for a single medication treating these co-occurring, simultaneous disorders despite there being at least a 50% overlap in them in the general psychiatric population. When randomized trials do not exist, prescriptions based on known neurocircuitry may lead to more accurate prescribing and better outcomes on a per patient basis. Obviously trials in this area, possibly aided by genetics and neuroimaging, may play out in the future.

MANUALIZATION OF PSYCHOPHARMACOPSYCHOTHERAPY

In the current outpatient treatment milieu, where the splitting of psychopharmacotherapy and psychotherapy is commonplace, many psychopharmacologists use FDA approvals and symptom-based approaches to treat MDD patients. Given the high noncompliance rates with psychotropics and office visits, it would make intuitive sense to see if true combination of pharmacotherapy and psychotherapy in a single sitting is truly effective management of the MDD patient.

If one were to conceptualize doing some psychotherapy in a 20- to 30-minute medication visit, many would be skeptical, as traditionally therapy occurs over a 50- to 60-minute session. Also, in psychopharmacology, visits tend to occur every one to six months in practice, and therapy may not be effective occurring so infrequently. A novel approach would be to train psychiatrists to see patients and utilize antidepressants initially to lower depressive symptoms at the outset (see sequential treatments mentioned earlier). Following this, sessions could be conducted more often as less attention could be paid to acute pharmacotherapy and more minutes dedicated to using core psychotherapeutic skills (as noted earlier) in lieu of a systematic manualized or nondirected supportive therapy. Hypothetically, these core skills could help build rapport, enhance medication compliance, and treat many residual symptoms without the need for additional polypharmacy. Training residents to become competent in core skills would be dramatically easier than training them to be competent in dynamics or CBT. The learning curve and mastery is simple, which would lead to continued use and further mastery. Measuring outcomes with clinician- or patient-rated scales would also be simple in this setting. This training would show the value of maintaining key psychotherapeutic values in all medication

management visits, which trainees would then continue in practice despite pressures to see more patients and provide complex polypharmacy. This "package deal" could assert that focusing on medications and psychotherapy simultaneously, tracking with rating scales, and evaluating one's own practice-based medicine while faculty measure competency is easy and worthwhile, and would lead to better patient outcomes and more clinician competency in providing medication and psychotherapy.

TECHNOLOGY AND SOMATIC TREATMENTS

As was reported in previous chapters, the advent of neuroimaging and neurogenetics is both fascinating and confusing. Both the techniques employed and the data collected are in their infancy and often conflicting in nature. However, great strides in the use of these techniques occur frequently. The ability to predict treatment response and choose the right modality first should be pivotal in treating an MDD patient. Similar to the pharmacodynamic theory that may be used to drive rational polypharmacy to alleviate particularly externally valid, phenotypic MDD symptoms, simple imaging or genetic testing may be able to tell us more quickly which internal neural systems are malfunctioning, and based on this, our initial treatment could be the ultimate treatment. This could alleviate many weeks of continued patient suffering, as multiple, "best-guess" drug trials could be alleviated.

As you will see later in the chapter, new, groundbreaking medications are few and far between. It appears we have entered the era of somatic and device treatments. In this book, electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), and transcranial magnetic stimulation (TMS) are discussed extensively, and all are now FDA approved. It is a shame that the latter two therapies are difficult to provide to patients because of their expenses and insurance companys' near-total refusal to cover these expenses. These devices are legitimately FDA approved, yet companies are allowed to decide on their own whether they are still "experimental." With few new mechanistic treatments available outside of the usual monoamine antidepressants, these devices should be applauded for their ingenuity and novel mechanisms of antidepressant action. This does not mean that the floodgates should be opened and every depression patient receive a device, but on the basis of the evidence those patients should be selected who are most likely to receive benefit and be given a chance at recovery.

Finally, we expect to see advances in the use of deep brain stimulation (DBS) and possibly cortical surface stimulators (9). These devices help in accessing the brain with electricity to change neurochemical transmission instead of the medication-induced chemical changes to induce electrical transmission changes. This fact grants these devices a very novel antidepressant mechanism. Similar to psychosurgery, which still continues at select institutions, these safer implantable devices may also be used to restore better communication between cortical and limbic structures and facilitate recovery from depression without the same level of risk.

TECHNOLOGY AND PSYCHOTHERAPY

Device-related treatment is not solely the purview of biological pharmacotherapy and psychiatry. Psychotherapists are also beginning to utilize devices, equipments, and computers for providing psychotherapy. On a basic level, CBT

lends itself to computerization. A few researchers have been evaluating if patients could sit with a computer for several sessions and be run through some routine CBT protocols where they are taught to monitor anxiety or depression levels, given some initial relaxation strategies or cognitive skills to counter against automatic negative schema, and also to create some minor desensitization strategies. Perhaps a computer could successfully treat minor levels of depression and anxiety, for instance. It is likely that CBT use of computers would be more in the "'computer-assisted" psychotherapy, where certain software programs are used to help create and police compliance with hierarchies, and measure effects of CBT treatment, instead of an artificially intelligent software system dictating therapy.

Virtual reality therapy (VRT) (10) currently exists for anxiety patients. In typical CBT, patients are given a hierarchy to engage in challenging their anxiety processes for desensitization purposes. This is ultimately conducted in vivo in the community, that is, for example, for fear of heights or airplanes the therapy patients are treated on a building or in a plane. The efficiency of VRT is that computer-simulated situations can be created in the safety of an office setting, and patients can be desensitized in a clinician's office. Patients wear goggles, which allow them to see a 360° computer-simulated image. If the patient turns his/her head, the image shifts. This is not unlike a high-end three-dimensional "first-person" video game that teenagers play and that ultimately uses the same programming. Scenarios exist for fear of flying, heights, insects, and public speaking along with several combat scenarios, that is, Vietnam War and Gulf Wars. To make the scenario more than just a visual experience, headphones provide sound and some setups allow for motion and sense of smell. Aromatherapy can be added where smells related to combat, that is, smoke and gunpowder, might be used. For motion, a patient is usually placed on a platform, which covers a subsonic woofer where sound generates vibration of the platform, that is, for fear of flying. Although not real, or in vivo, VRT allows the next closest option, which is more efficient and less anxiety provoking than the in vivo process. VRT is targeted mostly for anxiety disorders. It could be used in anxiety comorbid with depression and would perhaps be a treatment of choice where the anxiety is premorbid and socially debilitating. Using VRT or other therapies to treat the anxiety could then possibly alleviate depression that may develop secondary to anxiety.

PHARMACOTHERAPY

Despite the serendipitous discovery of the monoamine-oxidase inhibitors in the 1950s and the tricyclic antidepressants in the 1960s, several specific pharmacotherapies have been developed for the treatment of MDD. Despite these advances, a significant proportion of patients who are treated for MDD remain symptomatic.

Clearly, greater research efforts are needed to further refine the treatment of MDD. Such efforts can be directed in one of three major areas: (*i*) the development of novel pharmacotherapies, (*ii*) the refinement of existing pharmacotherapies and pharmacotherapeutic strategies, and (*iii*) the identification of biological as well as clinical factors, which may help define a subgroup of MDD patients who are particularly responsive to certain treatments. Much of these new options have been covered in previous chapters. Triple monoamine

reuptake inhibitors of serotonin, norpeinephrine, and dopamine reuptake pumps are being studied. Unique pharmacodynamic profile antidepressants are being studied, that is, agomelatine's blockade of serotonin-2 receptors and stimulation of melatonin receptors. Hormonal and nonmonoamine treatments are relatively scarce in practice and in the literature. Cortisol-dampening products have shown some efficacy in psychotic depression. Glutamate may be the transmitter we approach next. Zarate's work with National Institutes of Health (NIH), for example, continues where ketamine and riluzole seem to exert antidepressant potential in depressed patients by dampening glutamate transmission (11). As we seem to have exhausted the monoamine approaches, these novel ones are warranted, as treatment-resistant depression seems to be more the norm than the exception in psychiatric practice.

We may also see the reemergence of medical foods and nutraceuticals. Evidence-based information continues to develop for folate, l-methylfolate, SAMe, and even perhaps the biopterins and other vitamins, that is, B_{12}. Many of these are involved in a cascade and are dependent on each other for optimal functioning. In theory, if these intertwined systems function well, neurons by way of enzyme activation may be given more ability to produce monoamines. The net effect is that we may be "priming the neuronal pump" in that we allow neurons to make more transmitters, which provide more substrate for our usual antidepressants to work with. A selective serotonin reuptake inhibitor (SSRI) in theory can only work if there is reasonable serotonin in the synapse to actually block serotonin reuptake. Many of our medications work in the synapse, where we assume there are enough transmitters to work with, and the medical foods, vitamins, coenzymes, etc., may become reasonable augmentation treatments to provide adequate transmitter levels.

USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE

Several complementary and alternative treatment options such as yoga, acupuncture, massage therapy, and herbal therapies have been used in the treatment-resistant depressive population. These latter were covered in a previous chapter. Approximately 75% of U.S. adults have used some form of complementary or alternative medicine (CAM), and 5% report anxiety or depression as a motivating factor. The practice of yoga has its origins in Indian culture, and it often comprises a complex system of spiritual, moral, and physical practices aimed at attaining self-awareness. It includes postures, breathing methods, chanting, and meditation. It may be a form of behavioral therapy from the relaxation point of view and possibly cognitive from the meditation and awareness point of view. Breathing helps focus and relaxation, whereas meditation aims to calm the mind as well. There are studies that found sudarshan kriya yoga (SKY) (12) breathing techniques to be effective in depression, where the author is currently a subinvestigator in a new protocol as well. An initial three-month, open pilot study of 15 patients with dysthymia and 15 with major depressive disorder showed significant reductions in both Hamilton Rating Scales for Depression (HRSD) and Beck Depression Inventory scores after one week of SKY training and three more weeks of daily practice. Streeter and colleagues (13) have conducted a study where brain γ-aminobutyric acid (GABA) levels associated with an acute yoga session increased after the session

of yoga and suggested that the practice of yoga should be further evaluated as a treatment for disorder with low GABA level such as depression and anxiety.

Using Eastern medication practices such as yoga and acupuncture may also become an additional option for depressed patients. Data are often of open-label nature, and funding for the CAMs is just starting to become available. Whether these techniques alter brain neurochemistry like medications or provide core psychotherapeutic techniques (cognitive awareness, behavioral modification, progressive relaxation, etc.) or have their own unique antidepressant effect is yet to be determined.

CONCLUSIONS

Over the past several decades, great strides have been made in our understanding of which psychotherapies are most effective for treating depression. We now have two primary evidenced-based psychotherapies (CBT and IPT) that are increasingly being practiced by mental health professionals throughout the world. Despite this progress, a multitude of questions remains unanswered. These include how to best apply these treatments, whether some of the more recently developed treatments that represent significant paradigm shifts will prove efficacious in larger studies, how to best adapt our treatments to patients with significant comorbidities, what aspects of depression are important to consider in selecting treatments, and how evidence-based treatments can best be disseminated to frontline treatment settings. Answers to these questions will help shape the field for the coming decades.

In parallel, we have many of the same questions and issues with regard to pharmacotherapy. There appears to be a pipeline dedicated to facilitating monoamine transmission and very few treatments that are "out of the box." With available resources we must get better at providing safer, more aggressive treatment for the MDD patient. This may include early and better detection with rating scales and improved training, use of imaging and genetics, and finally rational polypharmacy to promote better effectiveness and tolerability.

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